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ORIGINAL ARTICLES

STUDIES IN TUBERCULO-IMMUNITY*†

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Efforts to produce immunity to tuberculosis by use of the tubercle bacillus or its products date back to the period of feverish activity immediately following Koch's discovery of that microörganism. These have covered a wide range which include many ingenious modifications of the bacillus, such as: 1) passage through refractory animals; 2) attenuation by time, dryness, chemicals, light, putrefaction, burial in the earth; 3) death by many different methods. Furthermore, inoculation of nonpathogenic acid-fast bacilli of varying origin came into wide use at one time.

But it remained for Trudeau in 1892[26] to demonstrate unequivocally that the only substantial and specific protective maneuver against tuberculosis brought out in the first decade following the discovery of the bacillus rested in preliminary inoculations of living, attenuated tubercle bacilli. This he did, first with avian bacilli, then later, in 1897, with human bacilli[27],

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following a demonstration made by De Schweinitz 3 years earlier, in which he used Trudeau's R_1 strain[5].

Other work followed which confirmed and extended Trudeau's observations. Notable among many stand those of von Behring[31], Nichols[21], Römer[24], Hamburger[11], Baldwin[3] and Krause[14]. Thus Calmette and Guérin's[4] studies on the attenuated bovine strain, BCG, seemed logical and received rather prompt recognition (and application by Weill-Hallé and Turpin[33]) as an immunological agent. Conflicting reports on BCG appeared, however, as numerous investigators presented the results of their work. Such have continued to the present; some observers recording a high degree of immunity from its use (Aronson[1], Aronson and Palmer[2], Ferguson[8], Heimbeck[13], Frappier and Panisset[9], Wallgren[32] and Rosenthal[25]). Others have denied any worth to the preparation (Petroff and associates[23], Levine and Sackett[16] and Palmer, Shaw and Comstock[22]). Still other workers have, with scientific logic, been dissatisfied with the methods of standardization in respect to viability and have attributed the differences to the great discrepancies in the ratio of living to dead bacilli in the inoculum (Vandiviere, Gentry and Willis[28]). Some have questioned whether such differences in result might inhere in the strain itself. Indeed, Dubos[6] has reported differences in results of vaccination that might well have represented differences in behavior of strains of BCG maintained by different laboratories. This hypothesis was in keeping with the protocol of the study reported in this paper.

To test whether immunogenic differences in various strains exist and to compare these cultures with each other and with the human strain R_1, experiments were contemplated, a grant from the National Tuberculosis Association-American Trudeau Society became available for the endeavor, and strains of BCG were obtained from four laboratories in this country and five abroad.* The human strain R_1 has been carried in animals by transfer for a period of 10 years, by means of passage from animal to animal, and without contact with culture medium the while, this to test whether protracted association with or prolonged life in animal tissues would stimulate the return of virulence (Willis[35]). Studies were worked out on the basis of cultural and biological behavior of the bovine and human strains.

As shown in some detail below, it became evident early in the study that there was not one but several strains of BCG in use throughout the world, all masquerading under one label (Melvin and Vandiviere[17], Vandiviere *et al.*[30]) and each subject to possible change in potency in the laboratory.†

*BCG strains from these several sources in Europe and this country have undergone extensive study. Out of the collected group, four, which demonstrate the range of differences shown in the groups, have been used throughout the series of observations. They are:

BCG No. 1, from the Tice Laboratories through courtesy of Dr. Sol Roy Rosenthal.

BCG No. 2, from the New York State Board of Health at the hand of Dr. Konrad Birkhaug.

BCG No. 3, from the Henry Phipps Institute through the kindness of Dr. Joseph Aronson.

BCG No. 4, from the Tice Laboratories also coming by way of Dr. Rosenthal (received fairly late in the course of the study).

R_1, from Saranac Laboratories through the courtesy of Dr. William Steenken, Jr.

†For instance, cultures carried on a given medium for a protracted period sometimes lose capacity to form cords or to maintain their erstwhile status as gauged by the omental index test. Animals inoculated with cultures in this stage maintain reaction to tuberculin for a shorter period. Conversely, other cultures have developed increase in potency in such circumstances.

Proof of this lay hidden beneath a multitude of experimental observations and errors which resulted in interpretation of varying degrees in the efficacy of BCG inoculation. Obvious also was the fact that a measurable standard of viability of suspensions stood as a *sine qua non* and that results from infection with various strains could not be properly assayed immunogenically until standardization allowed duplication of exact dose of the several cultures, so that groups of animals could be inoculated simultaneously with suspensions predetermined to contain approximately equal numbers of living bacilli. It was not until a means of true standardization came to hand, therefore, that BCG from various laboratories could be compared one with the other and with R_1. Once it was possible to use standardized (equal) doses of living bacilli for inoculation, groups of animals could be inoculated, each group with its own strain, and subjected subsequently to challenge under a number of specific circumstances. This allowed for quantitative comparisons between strains and between inocula.

Methods. STANDARDIZATION. In order to fulfill the initial aim of the study, which was designed "to evaluate comparatively BCG and R_1 as immunological agents," it was necessary first to establish a baseline for each strain to be studied and to develop satisfactory methods of standardizing the preparation. Standardization of viability and of potency (degree of attenuation, or virulence) (Middlebrook[18]) in suspensions of *Mycobacteria* has long been an enigma of import, both procedures requiring long periods of time, and thus measurable in retrospect only and after studies were under way. By two separate tests developed in this laboratory, the time required for determining viability testing has been reduced to 4 hours, and for potency to 14 days. These tests are:

1) *Standardization of viability.* The first criterion of standardization, that is, viability, has, in the past, been dependent on colony counts, which require several weeks following preparation, for growth and interpretation. Time now required has been reduced to a few hours on the day the inoculum is prepared, by the development of a relatively simple but tedious chemical test based on the reduction of 2-3-5 triphenyl tetrazolium chloride to red formazan by the viable, metabolizing organisms (Vandiviere, Gentry and Willis[28]). This chemical process of reduction becomes also an indicator of the degree of viability of the bacilli in a suspension. Knowledge of viability is thus available *before* use of the suspension. These tests are made on cultures grown in Tween albumin medium (Vandiviere, Gentry and Willis[28]) and under the necessary *standard* conditions. In addition the cells present are measured by direct counts with a counting chamber (Krohn[15]) and by determination of turbidity and total wet volume (Hopkins tube). Relative counts of living and dead cells are made, utilizing a staining compound "p-Nitrophenyl ditetrazolium" (Nachlas *et al.*[20]). Thus there is obtained a total count, a viability count and a viability per cent count. Viability is "confirmed" by colony counts which are read 21 to 28 days later.

Concentrations of red formazan expressed in micrograms per milliliter fall in a straight line curve as shown in Fig. 1. Cultures of tubercle bacilli, subjected to tetrazolium (Vandiviere, Gentry and Willis[28]), range themselves along this line according to the intensity of the color produced by reduction. Repeated checks by colony count confirm their content of living bacilli. By such comparison, the degree of viability, numbers of living cells, can be determined by the intensity of the color and thus the place in the scale.

2) *Standardization of potency (virulence or attenuation).* One of the interesting features of Koch's discovery of the tubercle bacillus rests in the fact that he used human serum in his media for growing bacilli, which, in such medium, laid themselves down in cord or rope-like formation, the bacilli often lying parallel to each other in the cords. In recent years Middlebrook, Dubos and Pierce[19] have centered attention on this phenomenon and have made meticulous observations upon cording.

The first measure of standardization of potency is an *in-vitro* test based on the capacity of a strain of *Mycobacteria* to form cords in Dubos basal medium with bovine albumin fraction V, human serum and varying concentrations of the dispersing agent, Tween 80 (Melvin and Vandiviere[17]). When the strains under study are grown on media to which varying amounts of Tween 80 have

been added, they lose their capacity to form cords in proportion to increasing concentrations of this ingredient in the medium. The higher the potency (or virulence) of an organism, the greater the concentration of Tween required to prevent cording, or to cause dispersion of the cords which would form naturally in the albumin-serum medium.

As illustrated in Fig. 2, this formation is maintained in cultures of R_1 to a definitely higher level of Tween than in BCG strains No. 3 and No. 4 and far higher than in BCG No. 1 while the virulent strain $H_{37}Rv$ and a wild strain show persistence of cord-formation still further up the scale of Tween concentration.

The second potency test is the so-called omental index (Han, Kelly and Woodruff[12]) which is based on the ratio of the weight of the omentum in grams to the weight of the guinea pig in kilograms, 2 weeks following the intraperitoneal inoculation of a quantitatively measured amount of a culture suspension (Vandiviere, Vandiviere and Willis[29]). In this test the several BCG strains and R_1 range themselves in an order (Fig. 3) in which correlation with cord-formation titer is good, those with lower potency in cord-formation lie low in omental response and those high in the one category stand high in the other. These two methods of virulence testing are illustrated in Figs. 2 and 3, and both compare equivalently with long-term animal studies.

Preparation of inoculum. Normally, stock cultures are carried on Löwenstein medium and are transferred to Tween albumin (bovine) medium preparatory to making the suspension to be used as the immunizing substance. Each of the BCG strains and R_1 thus transferred grows for 8 days and is transferred again to the same type of medium. Eight days later the third transfer is to this medium in which human fraction V albumin has replaced bovine albumin. When these latter cultures have reached the age of 8 days, they become the material used for final preparation. The supernatant (without tubercle bacilli but with the bi-products of growth) is replaced by a fresh solution of

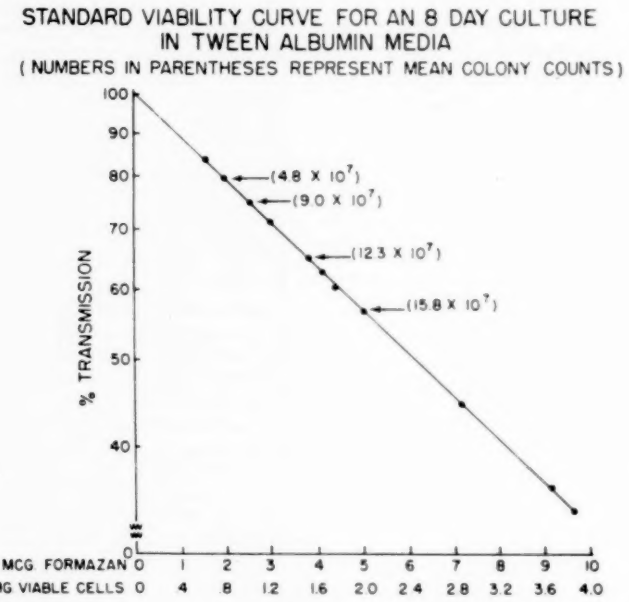


Fig. 1.—The viability or total number of living cells may be determined from the reduction of colorless 2,3,5 triphenyl tetrazolium chloride to red formazan by the metabolic activity of the living organisms. This is a rapid chemical test (requiring only 2 hours) which may be done at the time of vaccine preparation rather than waiting for colony counts. Under carefully standardized conditions, it has correlated well with colony counts, with less variation and more accuracy.

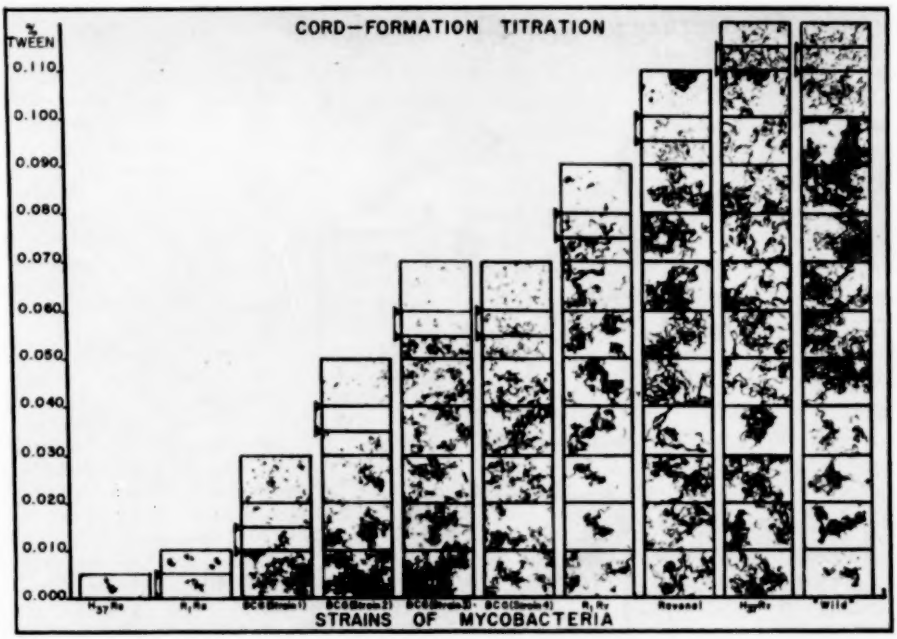


Fig. 2.—A graphic, pictorial representation of avirulent, attenuated, and virulent strains of mycobacteria demonstrating their specific capacity to maintain cords in increasing concentrations of "Tween 80." The end point or titer of each strain is indicated by [. The photomicrograph above the indicated end point illustrates the Tween concentration of significant dispersion (22 ×).

This figure is reproduced by courtesy of the Editor, American Review of Tuberculosis and Pulmonary Diseases.

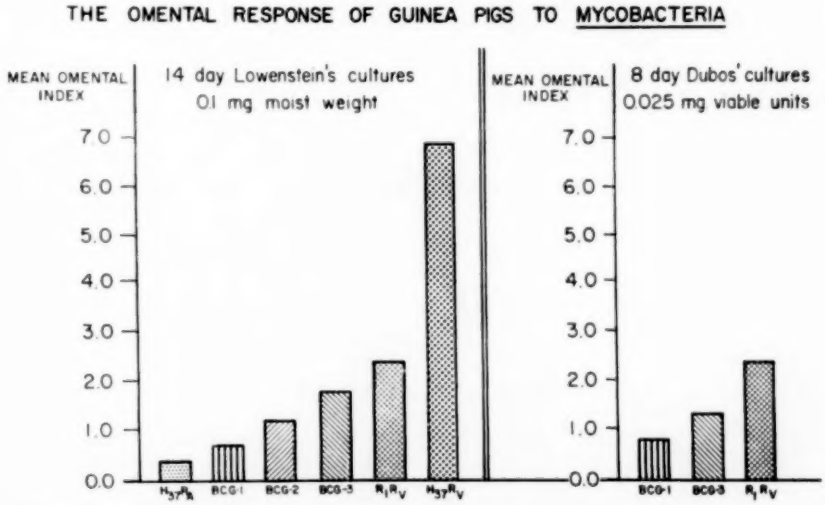


Fig. 3.—The omental response of the guinea pig to equivalent inocula of *Mycobacteria* indicates differences in the potencies of the strains tested. The index of R_1 was significantly lower than virulent $H_{37}Rv$, but higher than the best BCG tested.

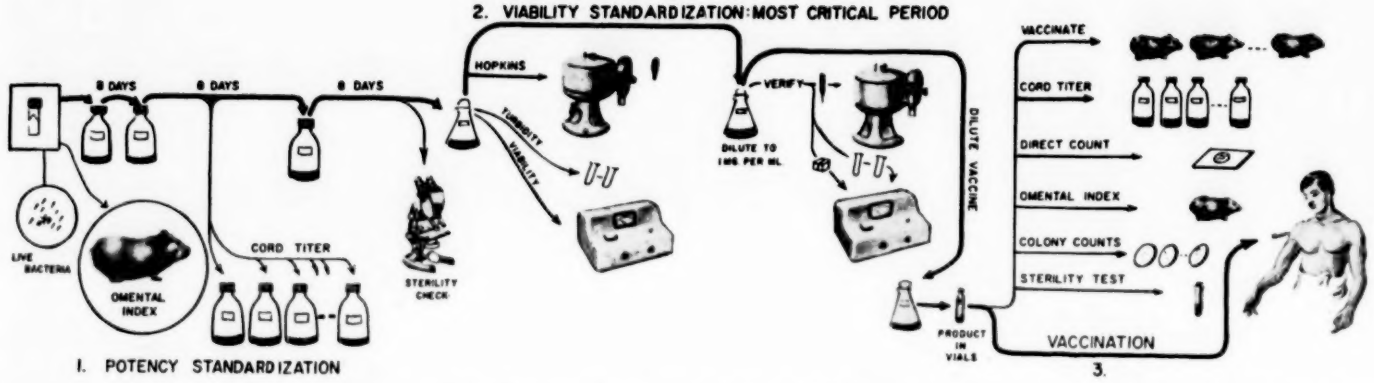


Fig. 4.—Chart showing various steps taken in preparing vaccine. These include standardization of potency and viability and procedures taken to insure purity.

salts with Tween and human albumin fraction, and this is used to make the final suspension. Samples are removed for tetrazolium reduction tests of viability and for turbidity, volume (Hopkins tube), test by direct count, and relative counts of living and dead cells after subjection to neotetrazolium. A preliminary standardization is made, adjusting the suspension to the transmission point on a standard curve suggesting 1 mg. of viable cells per milliliter of suspension. After dilution is made, the tests are repeated for confirmation of the above results, and prediction, the final step of the preparation, is either complete at this juncture, or another dilution may be necessary for the desired concentration. Colony counts are made for confirmation. Omental index and cord-titration are repeated, and groups of guinea pigs are inoculated, each with its assigned strain for further controlled study or evaluation. This procedure is illustrated in Fig. 4.

Comparison of results of protective inoculation by several strains of attenuated Mycobacteria. Allergy to tuberculin tends to wane and disappear (Willis[36]) as the infecting bacilli lose their invasiveness or as they disappear from the body, and only transient allergy follows injection of killed bacilli. Inoculation with killed tubercle bacilli leads to sensitivity which, even if vigorous at first, fades within weeks and disappears within several months.* Also, nonpathogenic acid-fast bacilli: smegma, phlei, and others, arouse transient sensitiveness to tuberculin. At disappearance of sensitiveness, bacilli may no longer be found in the animal's body. This has been well shown recently by Gentry[10].

Results. Inoculation with the several strains of BCG under study yields allergy of differing duration and intensity. As shown above, standardization allows ready reproduction or duplication of dose of the several cultures so that groups of animals may be inoculated with suspensions or vaccines, each with approximately equal numbers of living bacilli. On this base line, then, standardization suspensions of R_1 and of various strains of BCG were inoculated in equisized dose, each into its own group of guinea pigs, for various short and long-term observations as to 1) the duration of allergy produced, 2) volume of allergic response, 3) degree and duration of protection conferred against challenge with approximately equal (but varying) numbers of viable tubercle bacilli of known virulence. Differences were marked.

After inoculation and careful description for certain identification, animals from all the groups were pooled and distributed so as to nullify influence of local environmental factors.

1) DURATION OF ALLERGY. In one experiment, four groups of normal, tuberculin-negative animals, each inoculated with the relatively small dose of 0.005 mg. of living bacilli of its assigned strain (BCG No. 1, No. 2 or No. 3 or R_1), were kept for 21 months. They received tuberculin tests periodically and, as shown in Fig. 5, they varied in the rate at which they lost their sensitivity. At six months 35% of the animals pretreated with BCG No. 1 no longer reacted to the usual test dose of 1:1000 O.T.; failure to react occurred in 5% of those given BCG No. 2, in 3% of the BCG No. 3 and in none of those receiving R_1. At 12 and 15 months some decline occurred in the curve of all groups, and at 21 months 64% of the R_1 animals had retained the capacity to react, 54% of those receiving BCG No. 3, 42% of those given BCG No. 2 and 27% of those which had been inoculated with BCG No. 1.

*There have been proponents and opponents on this issue. Claiming loss of hypersensitiveness fairly promptly are, among several others: (1) **Crawford, A. B.:** J. Am. Vet. Med. Assn., **44,** (new series **17**), 228, 1923; (2) **Selter, H.:** Deutsche med. Wchnschr., **51,** 933, 1925; (3) **Selter, H.,** and **Geschke:** Ztschr. f. Hyg., **102,** 303, 1924; (4) **Lange, B.:** Beitr. z. klin. Tuberc., **67,** 307, 1927.

Some opponents to the view of prompt loss of hypersensitivity are: (1) **Petroff, S. A.,** and **Stewart, F. W.:** J. Immunol., **10,** 677, 1925; (2) **Petroff, S. A., Branch, A.,** and **Jennings, F. B., Jr.:** Ibid., **16,** 233, 1929; (3) **Zinsser, H., Ward H. K.,** and **Jennings, F. B., Jr.:** Ibid., 10, 719, 1925.

2) VOLUME OF ALLERGIC RESPONSE. Similar variation and similar fall-off in the size of the tuberculin reaction occurred in the groups of animals inoculated with the several strains. Figure 6 illustrates the reduction in volume of reaction and indicates that the animals retaining allergy in the largest numbers yielded the most lusty reactions and presented the largest volume of reaction, BCG No. 1 and R_1 standing at the extreme of small and of large response.

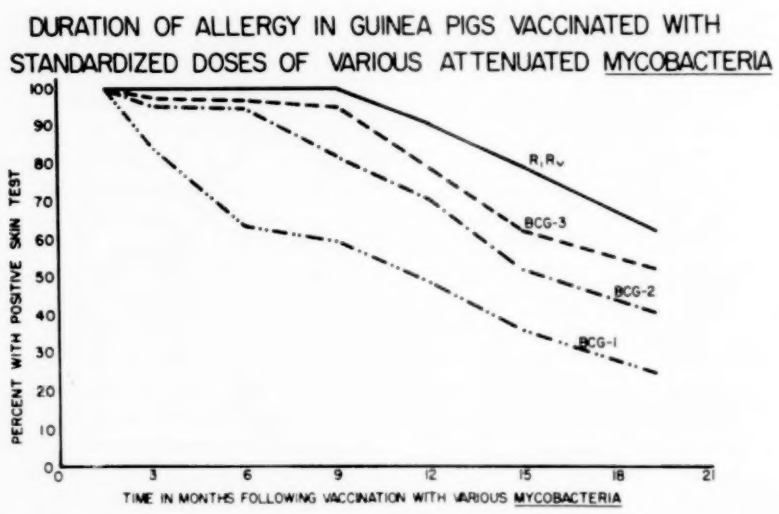


Fig. 5.—Suspensions of attenuated tubercle bacilli (BCG No. 1, No. 2 and No. 3 and R_1) inoculated in their designated groups of animals produce tuberculin reaction which lasts a shorter time in some than in others, BCG No. 1 falling off faster and R_1 slower than the others.

Now the interesting and significant features about these reactions is that the ascending scale of biological response, BCG No. 1 to R_1, as shown in the duration and extent of tuberculin reaction in animals inoculated with the strains, corresponds to the ascending scale of cord-formation and of omental index. The weakest of the BCGs (namely BCG No. 1) stands lowest in the titer of cord-formation and lowest in omental index. R_1 is highest in all these areas of comparison, with BCG No. 2 and No. 3 intermediate. These relationships stand out in the composite diagram (Fig. 7) to which also has been added the degree of protection against challenge offered by these several vaccinating agents. This latter feature is represented as Feldman's Index and applies to the response of the groups of inoculated animals to challenge with virulent bacilli ($H_{37}Rv$ in equisized dose for each group). It was because of the accuracy of these data on cord-formation and omental response in detecting the degree of proved potency that these two tests were selected as methods of potency standardization.

In the Feldman Index[7], values are given on the basis of distribution of lesions and the degree of visceral involvement. The scheme allows 100 points for "total" involvement, the points being 35 for extensive disease, 20 for moderate and 10 for slight for the various organs (not to exceed 100, as indicated). It thus stands as an

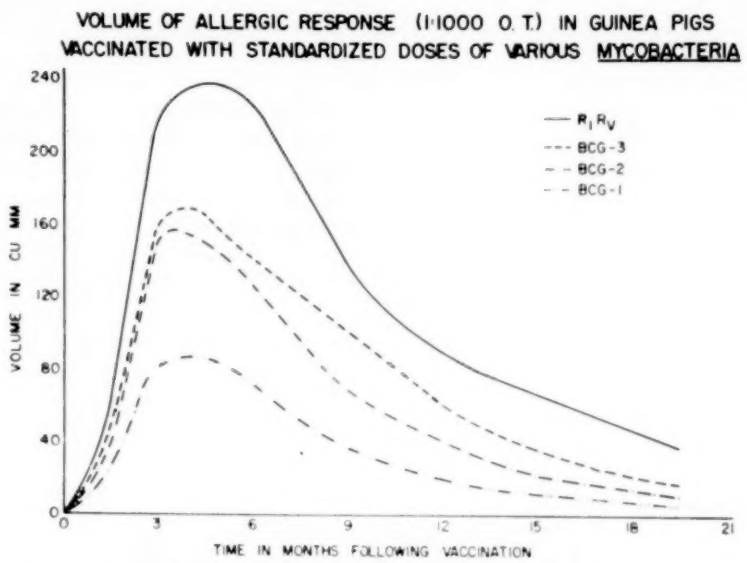


Fig. 6.—The volume of allergic reaction in animals inoculated with the several strains varies in correspondence with the differences in duration of allergy shown in Fig. 5.

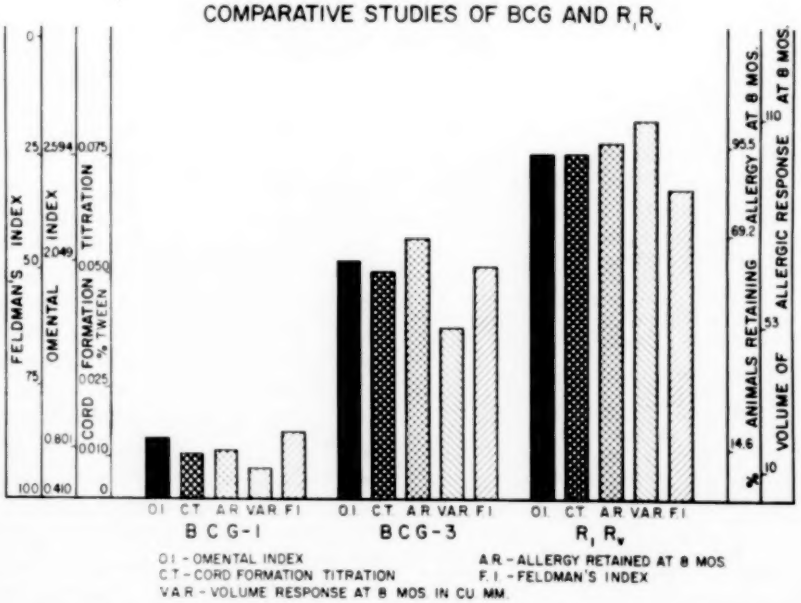


Fig. 7.—Comparison of three attenuated strains shows correlation by the various methods of testing, with the lowest values for BCG No. 1, intermediate for BCG No. 2 and highest for R_1, corresponding to relative degree of protection they provide.

excellent over-all measure, but it allows registration of small lesions in the lymphoid tissue tributary to the site of inoculation and in the tracheobronchial nodes to loom disproportionately large in designating disease in animals which, after protective inoculation, may present no disease in sites other than these.

3) DEGREE AND DURATION OF PROTECTION CONFERRED BY INOCULATION: *Comparison of results from inoculation with the several strains.* Protection experiments have run the gamut in dose, in time and in challenge. Out of a welter of observations which have required the use of approximately 7,000 animals, representative experiments are presented as illustrative of the principles involved.

It is obvious that results will be modified by variations in dose of protective inoculum; in time between such inoculation and challenge and in the challenge dose itself. These factors are taken into account in the following representative experiments. In these, "short-term" vaccination implies the lapse of 6 months between introduction of the protective inoculum and the test or challenge by living, virulent bacilli: "long-term" implies that such a period of time covers a minimum of 12 months, with experiments ranging from 12 to 30 months from vaccination to challenge. These several experiments will be presented in more detail later.

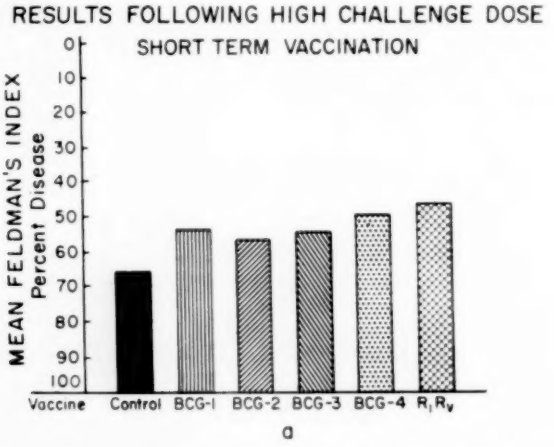


Fig. 8.—Short term vaccination (6 months): challenge by high dose. Such over-challenge masks differences and does not allow quantitative comparisons of resistance among the several groups. Based on data presented in Table 1.

TABLE 1.—SHORT TERM VACCINATION—CHALLENGE WITH LARGE DOSE.

Type Vaccine	*Mean Feldman's Index*	*Comparative Evaluation*		
		d.f.	*t.*	*P*
Control	66 ± 20	73	2.041	<0.05
BCG 2	57 ± 20	91	0.714	>0.05
BCG 3	54 ± 18	93	0.250	>0.05
BCG 1	53 ± 18	91	0.877	>0.05
BCG 4	49 ± 16	89	0.526	>0.05
R_1	47 ± 17			

Although all vaccine strains afforded some protection when compared with the control (as shown by the significant difference between the poorest group and the controls), no real differences could be demonstrated between strains.

a) *Short-term vaccination: challenge with large dose.* In this experiment 261 guinea pigs were separated into 6 groups (including 24 used as controls to the challenge). Each of the groups received a dose of 0.025 mg. viable bacilli of its designated strain and was tuberculin-tested at predetermined intervals thereafter. At the end of 6 months, all groups were inoculated with a suspension of viable bacilli of the virulent strain, $H_{37}Rv$, in the large dose of 9×10^5 (900,000).

At termination of the experiment 4 months after challenge, necropsy revealed extensive disease in all animals ranging in the Feldman Index, as shown in Table 1 and Fig. 8.

This indicates that a dose of this magnitude tends to overwhelm immunity. Under these circumstances only a very moderate degree of protection is manifest, and very little difference in immunity is detectable between the groups inoculated with the several protective strains, those in the R_1 group showing the best, but still poor, results.

In addition to the experiment just cited, 432 guinea pigs, in various groupings respecting vaccination with higher doses of 0.1 and 0.2 mg., were challenged at doses of 8×10^5 and 9×10^5. Results similar to those above were the outcome, showing again that overwhelming dose masks even what has later proved to be a relatively high grade of immunity.

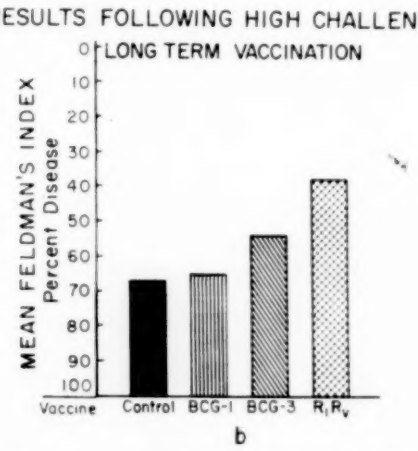


Fig. 9.—Long term vaccination (12 months): challenge by large dose. Differences between groups of animals, each protected by a different vaccine were detectable but not significant. Graphic representation of data shown in Table 2.

TABLE 2.—LONG TERM VACCINATION: CHALLENGE WITH LARGE DOSE.

Type Vaccine	*Mean Feldman's Index*	*Comparative Evaluation*		
		d.f.	*t.*	*P*
Control	68 ± 21			
		53	0.750	>0.40
BCG 1	65 ± 22			
		59	0.961	>0.30
BCG 2	60 ± 19			
		68	1.600	>0.05
BCG 3	52 ± 19			
		57	0.344	>0.70
BCG 4	50 ± 24			
		55	2.241	<0.05
R_1	37 ± 18			

Vaccine strains BCG No. 3, BCG No. 4 and R_1 offered protection of significance. When compared with the control group, all demonstrated P values of <0.01. The weaker strains offered little protection, and no real differences could be shown when comparing strains except in one instance (between BCG No. 4 and R_1).

b) *Long- term vaccination: challenge with large dose.* To test the effect of long-term protection against heavy challenge, 172 animals were divided into 6 groups, one for control; the others, each for inoculation with 0.025 mg. of viable attenuated bacilli of its designated strain which, in this instance, were BCG No. 1, No. 2, No. 3 and No. 4 and R_1. Twelve months later they were challenged with virulent $H_{37}Rv$ in the dose of 9×10^5 viable bacilli (900,000). Necropsy examination 3 months later (which represents the time at which one-half of the animals in the control groups had died)

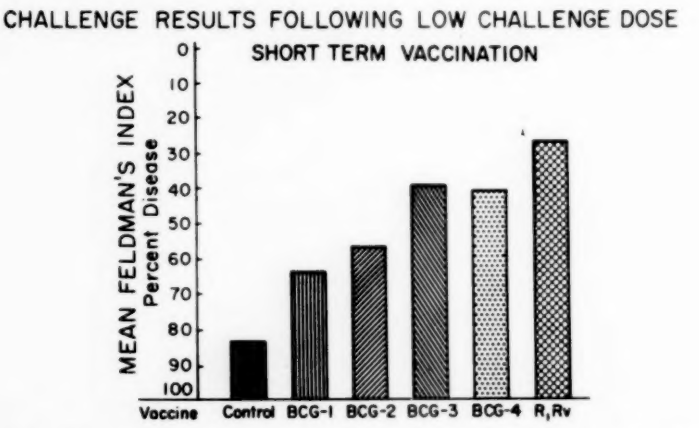


Fig. 10.—Short term vaccination (6 months) and moderate or small dose challenge. These relationships allow detection of differences among the groups and evidence of considerable protection in the animals vaccinated with BCG No. 3 and No. 4 (more) by R_1. Constructed from data in Table 3.

TABLE 3.—SHORT TERM VACCINATION: CHALLENGE WITH SMALL DOSE.

Type Vaccine	*Mean Feldman's Index*	*Comparative Evaluation*		
		d.f.	*t.*	*P*
Control	83 ± 18	58	3.454	<0.01
BCG 1	64 ± 22	78	1.200	>0.20
BCG 2	58 ± 20	74	3.166	<0.01
BCG 3	39 ± 25	63	0.188	>0.90
BCG 4	40 ± 16	52	3.250	>0.01
R_1	27 ± 13			

In this short term experiment, all the strains of vaccine tested provided good protection. When the poorest is compared with the control animals $P<0.01$. Certain strains provide greater protection than others as illustrated by the significantly greater protection afforded by BCG No. 3 or BCG No. 4 over either BCG No. 2 or BCG No. 1, and R_1 over the best BCG (In each case $P<0.01$).

showed a moderate degree of protection. Figure 9 provides graphic representation of the results and is based on data assembled in accordance with the Feldman Index shown in Table 2. Figure 9 presents results shown by 4 of the 6 groups included in the accompanying table. These results suggest that greater protection is conferred by R_1 than by the several BCG strains, but exemplifies the difficulty in demonstrating differences between the degree of protection afforded by the several vaccines against overwhelming challenge dose.

3) *Short-term vaccination: challenge with small dose.* The 875 guinea pigs in this experiment were divided into 6 lots: 5 for inoculation with equivalent

milligrams of viable attenuated bacilli and one for control. (Doses of each strain were 0.025, 0.05, 0.1 and 0.2 mg.) These doses were distributed among the 5 lots of animals so as to provide comparable numbers of animals under comparable doses. Lots BCG No. 1, No. 2, No. 3 and No. 4 and 0.05 and 0.20 mg. was used in groups of guinea pigs receiving BCG No. 1, No. 2 and No. 3 and R_1 respectively. The period between vaccination and challenge ranged from 18 to 30 months,* and the challenge dose was reduced to 3×10^4 (30,000 bacilli) in some lots and 6×10^4 (60,000 bacilli)

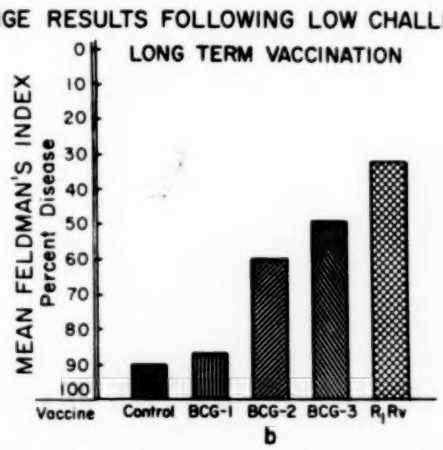


Fig. 11.—Long term vaccination (30 months) followed by small dose challenge. Here difference in degree of protection displayed by the several groups of guinea pigs is quite obvious and statistically significant.

R_1 received their proper dose of their designated strain. Six months later, challenge occurred in all groups with a dose of living, virulent $H_{37}Rv$ in the amount of 9×10^4 (90,000 bacilli).

The experiment came to an end 6 months after challenge. Results are shown in Fig. 10 for the controls and 5 lots of animals which received the immunizing dose of 0.05 mg. As Table 3 shows, a considerable degree of protection is exerted by all the strains, notably by R_1 and BCG No. 3 and No. 4.

d) *Long-term vaccination: challenge with small dose.* In this illustrative experiment involving 316 animals, live inoculum in concentration of 0.025,

TABLE 4.—LONG TERM VACCINATION: CHALLENGE WITH SMALL DOSE.

Type Vaccine	*Mean Feldman's Index*	*Comparative Evaluation*		
		d.f.	*t.*	*P*
Control	90 ± 12			
		37	0.800	>0.40
BCG 1	86 ± 18			
		44	5.421	<0.001
BCG 2	59 ± 20			
		47	2.127	<0.05
BCG 3	49 ± 18			
		44	3.333	<0.001
R_1	33 ± 13			

The varying degrees of protection produced by the vaccines are best illustrated by small challenge following long term vaccination. Under these quantitative conditions, the weakest (BCG No. 1) provides no essential protection. The others tested provided good protection. Significant differences are shown between the vaccines, with R_1 offering by far the best protection.

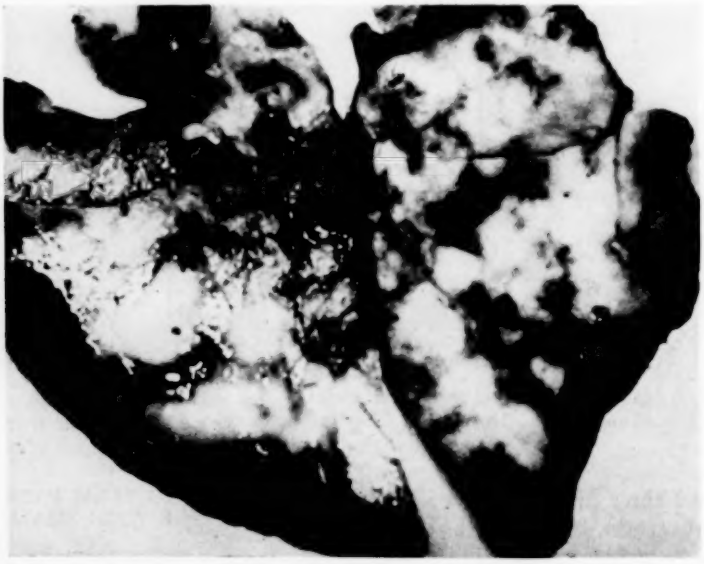
*Protective vaccination in this experiment covered a period of 30 months except in a few groups in which it stood at 18 and 21 months.

At 5 months after challenge, one half of the control animals had died. The experiment was terminated at that time and gross pathological comparisons made.

in others. The groups of animals, presented in Fig. 11 and Table 4 and discussed below, were those receiving vaccinating dose of 0.20 mg. and challenged with 30,000 bacilli. Challenge doses were so given as to be comparable among groups vaccinated with the varying doses.

The experiment was terminated 5 months after challenge inoculation, at consideration of pathological implications. Those having received BCG No. 2 revealed a good deal of tuberculosis but distinctly less than the BCG No. 1 group, the BCG No. 3 group still less, and the R_1 groups presented only slight involvement.

The pathological response. The pathological evidence on which the above deductions have been based



Figs. 12 to 16—represent the average response to challenge with virulent bacilli ($H_{37}Rv$) in animals after long term (30 months) protective inoculation of 0.20 mg. of the several strains, each into its designated group of animals.

Fig. 12.—Representative control, non-vaccinated animal. Extensive, widespread caseous consolidation occupies almost the entire body of the lungs. The whitish, grain-like shadows represent high-lights.

a time when one-half of the control animals had died. Results were clear-cut (Fig. 11 and Table 4). Control animals and those "protected" by previous inoculation with BCG No. 1 were sated with tuberculosis. The latter in reality were no better than the control animals which were "vaccinated" with the vehicle used for suspending the organisms that were put into other animals. This will be shown below in stood out clearly in each of these illustrative experiments. Representative tissues are reproduced in Figs. 12 to 16. This series has come from the long-term study in which all the animals of each group received a constant dose of 0.20 mg. inoculum specific for the group (that is, BCG No. 1 to one group, BCG No. 2 to another and so on for BCG No. 3 and for R_1) and, after 30 months, were tested with low chal-

Fig. 13.—Representative from group "protected" by BCG No. 1. Almost total destruction of both lungs, looking as completely involved as the control, non-vaccinated animals (Fig. 12).

Fig. 14.—From the group protected by BCG No. 2, this representative lung contains numerous circular or globular areas of consolidation but obviously less than the group receiving preliminary inoculation of BCG No. 1. In this group the tracheobronchial lymph nodes are enlarged and caseous at points.

lenge dose (30,000 bacilli) which is believed to far exceed or, at most, approximate relationships encountered in nature. In each instance a section or slab 3 to 5 mm. in thickness has been prepared which shows a cut through the mid-portion of the lungs, the section extending through the width of the two organs from parietal pleura to parietal pleura and including the bifurcation.

Figure 12, showing disease so widespread that scarcely any normal lung tissue is apparent, is from an average animal in the control group. There is extensive consolidation and caseation but no gross cavitation.

Figure 13, represents a picture usual in the animals that had received earlier and presumed "protection" through inoculation with BCG No. 1. Here extensive and widespread caseation has given way to large areas of bilateral cavitation, not unlike that seen in fulminating pulmonary tuberculosis in man.*

Fig. 15.—That BCG No. 3 confers considerable protection is shown in this comparative section which is representative of the group thus protected and which presents but one focus of consolidation with central excavation, and enlargement of the tracheobronchial nodes.

From animals protected by BCG No. 2, sections show (Fig. 14) that considerable disease exists in the form of scattered, nodular areas of consoli-

*It should be stated that BCG No. 1 is no longer used as a vaccine and has been replaced by BCG No. 4 in this study.

dation; if not caseation, and distinct enlargement of the tracheobronchial lymph nodes that harbor focal necrosis. Lesion is definitely less than that shown in the BCG No. 1 group (Fig. 13).

A typical amount of involvement in the animals receiving BCG No. 3 is revealed in Fig. 15. Here there are fewer and smaller lesions and moderate enlargement of the tracheobronchial lymph nodes, without gross signs of necrosis.

Finally, Fig. 16 presents the typical appearance in the animals having had vaccination with R_1. Slight enlargement of a tracheobronchial lymph node or an occasional very small histologic tubercle is all the abnormal tissue to be found in the group.

Discussion. From these results it becomes obvious that manipulation of dose and of time-relations in a scheme of inoculation for protection against tuberculosis may produce a vagary of immunological result that ranges from near zero to well-nigh complete protection, as has been claimed many times in the literature on clinical application of BCG.

No technique yet devised and no degree of vaccination acts to protect completely against extremely large numbers of virulent tubercle bacilli. As in two of the cited experiments, it is easy to show that efforts at producing

Fig. 16.—This section is representative of the average response in the R_1 group of animals. No gross parenchymal lesion is visible. One tracheobronchial lymph node is moderately enlarged and presents minimal central necrosis.

If this specimen be compared to the preceding figures, the difference becomes obvious.

immunity against tuberculosis can be almost entirely negated by overwhelming challenge dose. Also, protection of moderate degree may present itself when relatively small doses (90,000) of virulent bacilli are used for challenge. Furthermore, the experiments quoted show the unusually high degree of protection that follows use of the more effective attenuated strains, and look ineffective. Thus the investigator must not only be forthright but must work with strain and dose of organism which will give comparative data that will allow selection of the best or most effective agent without bias. Choice of interval is important and selection of challenge dose should be near the anticipated exposure dose under natural conditions.

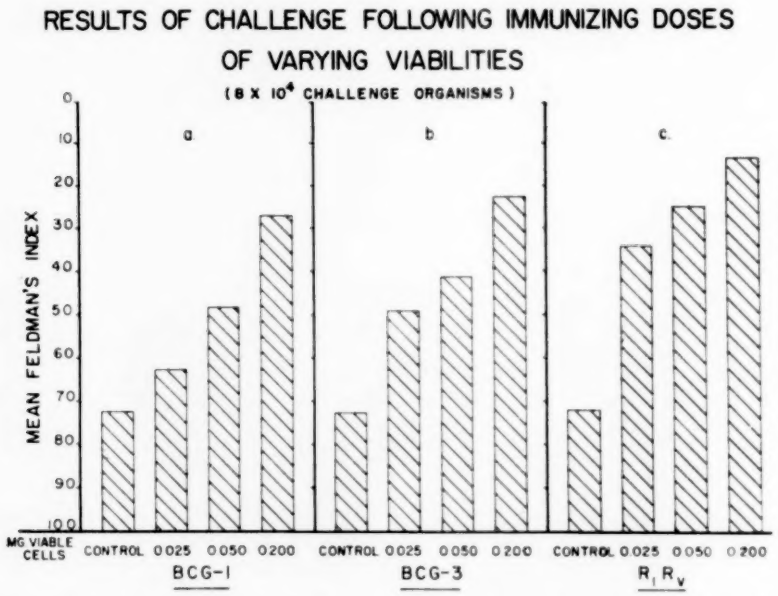


Fig. 17.—To increase the total number of weak organisms considerately beyond that of a strong organism will allow interpretation of equivalent protection if they are evaluated soon after vaccination. But this does not last. *To increase the viability will not compensate for higher potency.*

smaller challenge doses (30 to 60,000) which, though relatively small, are still in all probability a good deal larger than any dose that could be expected to arise from natural exposure.

It can be said, therefore, that, with this knowledge of tuberculo-immunity produced by living *Mycobacteria,* it is possible to make any vaccine look effective experimentally or to make any

One additional comment seems in order and this refers to the comparative capacity of so-called "weak" and "strong" strains. A large dose of weak organisms such as BCG No. 1 will, for several months, provide almost as good protection as a much smaller dose of strong organisms (R_1 or BCG No. 3 or No. 4). But, after such a relatively short period, the natural host-resistance will kill off the weak so that the in-

creased protection is relatively transient and short-lived. Part of the increased protection observed in such short-term experiments as those just cited may be derived from the relatively short period between vaccination and challenge. But another likely and important factor is obvious, namely the moderate size of the challenge dose (Fig. 17). Yet it should be remembered that, if challenge were postponed, as in some experiments (below), the weak strains lose their protecting capacity.

With higher doses of low-potency strains exerting short-term protective effect, it seems clear that potency of a strain stands as the determining factor in producing effective protection of practical duration. On this basis, then, one should be able to anticipate a degree of protection which reflects potency and thus be enabled to choose the immunizing agent having prolonged effect. That potency reflects itself in duration and degree of protection is seen in experiments cited.

Summary and Conclusions. The question of conferring immunity to tuberculosis has been debated for a long time, with proponents and opponents of the proposition marshaling facts and "citing scripture to the cause." The basic mechanism of operation of immune processes remains undisclosed, but techniques for eliciting protection are at hand.

From these studies it appears that preliminary inoculation of certain strains of attenuated tubercle bacilli creates a high degree of immunity which continues for at least as long as 30 months and is thought to be essential to prolonged protection.* Numerous strains have been used to this end with varying claims of efficacy. Comparison of several such for determination of their immunological effectiveness has been made possible only through establishing a method of measuring the approximate numbers of living bacilli in vaccinal suspensions, which is done through the use of 2-3-5 triphenyl tetrazolium chloride, a waterclear dye which is reduced to red (red formazan) by the metabolic processes of living cells and thus becomes an indicator of the degree of viability in the suspension under study (Vandiviere, Gentry and Willis[28]).

The bovine culture, BCG, has been subjected to analysis, with the result that there is not one BCG strain but several strains of widely varying potency or degree of attenuation and differing capacity to produce protection and duration of protection. Methods have been presented for classifying these various strains, demonstrating the range of their several, divergent potentialities in producing immunity, and the several strains of BCG having been compared with the attenuated human strain, R_1. Such comparisons, as a basis for study, have included:

1) Titration of cord-formation in culture growth in liquid medium containing varying concentrations of the wetting agent, Tween 80, which shows wide divergence among the BCG strains and between these and the R_1 strain and indicates the potency and thus the selection of the optimal strain; 2) The omental index, which is the measure of potency or invasiveness of strains 2 weeks after intraperitoneal inoculation, is expressed as the ratio of the weight in grams of the affected omentum to the weight of the guinea pig in kilograms. This likewise has turned out to be an excellent index

*In this connection Weiss[34] has recently published an elaborate treatise on protection with nonliving vaccines, in which he has reviewed many experiments to support the idea that protection may thus be produced. He has given an exhaustive and, apparently, all inclusive bibliography on the subject.

of potency and thus of selection of the immunizing strain of choice (Vandiviere, Vandiviere and Willis[29]); 3) The duration of allergy after inoculation into animals and the volume of the allergic response which stand as measures by which to classify the strains.

All three of these categories of classification tend to group the strains in such a way that those low or weak in one category likewise lie low in the other categories and those high in one category remain high in the others. (Fig. 7).

4) The protection afforded animals by inoculation of strains varies with the strain and its dose and duration of inoculation period prior to challenge as well as with dose of challenge infection. It is shown very clearly that it is possible to "prove" that a vaccine is no good by using an overwhelming dose in the challenge, because protection in the most favorable combinations and circumstances is not perfect. Also, by proper strain and dose, duration of time between vaccination and challenge and by use of a moderate challenge dose (thought almost always certain to be distinctly larger than that encountered in natural contact), a very high degree of protection will follow.

The highest degree of protection presented comes from use of the attenuated human strain R_1. Fairly close to this stand BCG No. 3 and No. 4. Other BCG strains studied fall far below this and exert little or no effect upon the course of infection following challenge.

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SUMMARIO IN INTERLINGUA

Studios in Tuberculo-Immunitate

Le question del establimento de immunitate contra tuberculosis es debattite depost longe annos, e proponentes e opponentes del idea insiste que "le factos" (e etiam le "textos sacrate") supporta les in lor attitude. Le mechanismo fundamental del processos de immunitate remane inexplicate, sed technicas pro obtener iste protection es disponibile.

Le presente studios pare indicar que un inoculation preliminari de certe racias de attenuate bacillos tubercular crea un alte grado de immunitate, le qual continua durante al minus 30 menses e es considerate como essential pro un protection prolongate.*

A iste fin numerose racias de bacillos ha essite empleate, con varie pretensiones de efficacia. Le comparation de plure de istos pro le determination de lor efficacia immunologic ha essite facite possibile solmente per establir un methodo de mesurar le numeros approximate de bacillos vive in suspensiones vaccinal, *i.e.*, per le uso de chloruro 2-3-5 triphenyl-tetrazolic, un tincto clar e aquose que es reducite a rubie (formazano rubie) per le metabolismo de cellulas vive e que assi pote servir como indicio del grado de viabilitate in le suspension que es studiate (Vandiviere, Gentry e Willis[28]).

Le cultura bovin BCG esseva subjicite al analyse, con le constatation que il existe non un racia unic de BCG sed plure tal racias, con marcate variationes in lor potentia o grado de attenuation e in lor capacitate de provider protection e le duration de illo. Es presentate methodos pro le classification de iste varie racias, demonstrante le extense spectro de lor potentialitates in le production de immunitate, e alora ille racias de BCG es comparate con le attenuate racia

*A proposito de isto Weiss[34] ha recentemente publicate un elaborate tractato super protection per medio de vaccinos nonvive. Ille ha revistate multe experimentos que supporta le idea que protection es producibile assi. Ille da un bibliographia extense e apparentemente complete.

human, R_1. Iste comparationes ha includite, como base del studio, le sequente procedimentos:

1. Titration del formation de cordas in culturas in un medio liquide continente varie concentrationes del agente molliante "Tween 80." Isto monstra un grande divergentia inter le racias de BCG e inter istos e le racia R_1. Illo indica le potentia e assi guida le selection del racia optimal.

2. Le indice omental, que es un mesura del potentia o invasivitate de racias de bacillos duo septimanas post inoculation intraperitonee. Illo se exprime como le proportion del peso in grammas del afficite omento al peso in kilogrammas del porco de India. Isto etiam se ha monstrate un excellente indice de potentia e assi del selection del racia immunisante de election (Vandiviere, Vandiviere e Willis[29]).

3. Le duration del allergia post inoculation in animales, e le grado del responsa allergic, le quales es etiam capace a servir como criterios in le classification del racias.

Le tres categorias de classification discutite in supra ha le tendentia de rangiar le racias de tal maniera que illos que es basse o debile in un categoria es etiam basse in le altere categorias, e illos que es alte in un categoria remane alte etiam in le alteres (Fig. 7).

Le protection accordate al animales per le inoculation con varie racias es variabile secundo le racia e le dosage e le duration del periodo inter inoculation e provocation e etiam secundo le dosage del infection provocatori. Il es monstrate con grande claritate que il es semper possibile "provar" que un vaccino es inadequate, simplemente per emplear un irresistibile dosage in le provocation; proque protection non es perfecte etiam in le plus favorabile combinationes e circumstantias. Etiam, per emplear le appropriate racia e dosage e duration de tempore inter vaccination e provocation e per le uso de un moderate dosage de provocation (que nonobstante remane plus grande que illos incontrate in contactos natural), un multo alte grado de protection va resultar.

Le plus alte grado de protection observate es illo obtenite per le uso del attenuate racia human R_1. Le racias BCG 3 e 4 ha un potentia non multo inferior. Le altere racias de BCG studiate es multo inferior a istos e exerce pauc o nulle effecto super le curso de infection post le provocation.

ESOPHAGEAL REFLEX ORIGIN OF MYOCARDIAL INFARCTION

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In the course of about one year, 4 patients were seen in consultation practice in whom the onset of myocardial infarction coincided with strong esophageal stimuli in conjunction with the process of ingestion. The abbreviated stories follow.

Case Reports. CASE 1. The patient, a clergyman age 54, had a healthy family background. He was chronically overworked, and he smoked cigarettes. His effort capacity was excellent, his blood pressure was normal. He had periodic episodes of abdominal distress that, as the course of events proved, were due to diverticulitis, resulting ultimately in an inflammatory-obstructive lesion of the sigmoid colon that required a surgical procedure. There never had occurred any swallowing difficulties. On May 3, 1959, he took a large ice-cold grape juice drink, almost immediately developed chest pain that extended from the center to the right shoulder and to both arms, and there was profuse sweating. He was hospitalized and the electrocardiographic study revealed a typical myocardial infarction pattern of predominantly diaphragmatic location. The patient felt well until June 15 when he developed chest pain. He was hospitalized again on our service. The findings were typical of the post-myocardial-infarction syndrome, with pneumonitis, pleurisy, pericarditis, and periostitis of ribs. The electrocardiogram showed essentially the same pattern as before. He ultimately made a good recovery. There was no anginal pain and there were no swallowing difficulties.

CASE 2. The patient, a storekeeper, age 63, was a cigarette smoker, overweight and had ankle edema. He had not experienced angina, either at rest, or in conjunction with exertion; but, as it was learned later, he had experienced mild chest distress on a number of occasions in conjunction with the drinking of ice water. He had not experienced swallowing difficulties. While exerting himself in the store on August 9, 1959, he experienced dyspnea that was associated wth slight sweating. Dyspnea occurred on two subsequent nights. An electrocardiogram was taken at the patient's home and inspection revealed the following abnormal findings: A rate of 100 per min., a Q deflection of 0.03 plus sec. in Leads II, III, V_5, and a small upward stroke in $V_{1,2,3,4}$, and deep S deflections in $V_{1,2,3}$, the S-T segments were a trifle elevated in Leads $V_{1,2,3,4}$, T was low positive in I, II, III, $V_{5,6}$, and positive in $V_{1,2,3,4}$. The patient was hospitalized on our service on August 11 and the essential findings were: Overweight, mild left- and right-sided congestive failure with Cheyne-Stokes respiration, enlargement of the heart with low-grade gallop rhythm, enlargement of the aorta with a systolic murmur and accentuation of the second sound, normotension, and mild diabetes. The roentgenographic study revealed some degree of pulmonary overfilling and some pleural fluid. There was no renal involvement. The blood serologic reaction was nonreactive. The patient was digitalized, received hydrochlorothiazide, and was placed on a diabetic diet and received Orinase. He improved, lost 16 pounds in weight, the heart rate slowed down, and in the roentgenogram the lungfields and pleural spaces appeared normal. At 9.00 p.m. on August 17, the patient drank ice-water and sucked on a piece of ice. He developed severe midchest pain that lasted for a period of 3 hours. An electrocardiogram taken in the morning on August 18 showed the following new abnormal findings: Initial deflection 0.11 sec. wide with Q deflections of 0.04 sec. width in II, III, aV_F, $V_{5,6}$, a Q deflection in I and aV_L, and a wide and deep QS in $V_{1,2,3,4}$, S-T arched and elevated in Leads I, $V_{1,2,3,4,5,6}$. T showed an incipient negativity in Leads $V_{4,5,6}$. The subsequent clinical course was uneventful. The follow-up electrocardiogram revealed regression of the S-T elevations and positivity of T in the left precordial Leads. There was no anginal distress and there were no swallowing difficulties.

CASE 3. This 60-year-old housewife had lost her mother and her brother in the thirties with heart conditions, an older sister

had suffered from angina and died with cancer. another sister had had several cerebrovascular lesions. The patient was known to have gallstones; otherwise she felt well, was free of the anginal syndrome and had no swallowing difficulties. When seen in the office on August 24, 1959, she gave the following information: Three and a half weeks prior she had an ice-cold drink. She immediately noted a sensation of a "lump" in the midsternal area, and this lasted for a period of 1½ hours. This sensation subsequently recurred when she walked up an incline on her street. A few days later, when walking toward the bus station there was a recurrence of about 8 minutes' duration. Next day, while drinking hot coffee, there developed severe chest pain that lasted off and on for a period of 4 hours and the pain radiated along the inside of both arms. Bedrest was then instituted and papaverine was prescribed. Nothing of significance was noted on examination. The electrocardiographic study revealed abnormal findings in that S-T was a trifle elevated in Lead aV_L and a trifle depressed in Leads II, III, aV_F, T was high positive in Leads II, III, aV_F negative in aV_L, and low positive in high Leads $V_{5,6}$. The electrocardiographic diagnosis was area of myocardial necrosis, high-lateral When seen again 2½ weeks later, the patient stated that she had been comfortable. The electrocardiogram revealed changes in that the previously noted S-T deviations had disappeared, the voltage of T had increased in Leads I, high $V_{5,6}$, and in Lead aV_L positivity of T had made its appearance.

CASE 4. This man, age 47, had lost his older brother with a myocardial infarction. He was a chain smoker of cigarettes, led an irregular life, played cards all night long, and he gulped his food. His effort capacity was good and he had no swallowing difficulties. One day about 5 months prior to the office visit, he swallowed a big piece of hot potato. He immediately felt that the bolus did not pass and there resulted a burning sensation that lasted for a period of several days. There was no radiation of the discomfort. There was no interference with the intake of food and liquids. On the third day, the family physician did an electrocardiographic study which was said to be nonrevealing. During the night of the fourth day the chest pain got worse, there was radiation to both arms and perspiration. A repeat electrocardiographic study the next day done by the family physician revealed the presence of a typical diaphragmatic wall infarction. Bedrest was instituted. Subsequently, a radiologic study of the esophagus, stomach and duodenum revealed normal findings. A further electrocardiographic study revealed regressive findings in the previously noted pattern of myocardial infarction. A recent history referred to several types of chest distress that were unrelated to the heart but there was also registered a complaint of a pulling or drawing sensation over the right and left anterior chest wall, occasionally across the chest, that was brought on when walking the distance of one or two city blocks, and relieved by rest. The clinical examination on May 12, 1959, revealed nothing of significance with respect to the heart, blood pressure, and the rest of the body, the serum cholesterol level was 275 mg. per 100 ml.

COMMENT. These 4 patients then had not experienced angina nor swallowing difficulties; one (Case 2) had noted mild chest distress on several occasions upon drinking ice-water. All 4 patients developed myocardial infarctions, as suggested by a typical history and as evidenced by electrocardiographic alterations. In 3 instances (Cases 1, 2, 3) this followed the ingestion of ice-old drinks, and in one instance (Case 4) this followed the lodging of a large piece of hot food in the esophagus. In 2 of the patients (Cases 3, 4) the subsequent clinical course revealed the presence of effort angina.

That deglutition of unusually cold or hot material is readily perceived is well known; heat may be felt all the way down; cold, however, is usually felt mostly at the lower end and is referred to the epigastric region in only a few seconds after the material is swallowed (Terracol and Sweet[6]).

Experimental data available in the literature and in some way related to the topic of this paper are as follows:

1. IN MAN. In the healthy person in recumbency, drinking of ice-water which accumulates in the fundus of the stomach, causes cooling off the posterior-inferior surface of the apical

region of the left ventricle and for a period of up to 10 to 15 minutes, conspicuous changes in the form of the T deflection of the electrocardiogram result, consisting of a decrease in the height of T in Lead II and inversion of T in Lead III, the form of T in Lead I not being altered (Wilson and Finch[9]). Identical experiments were carried out, using limb and unipolar limb Leads and Leads $V_{1\text{-}2\text{-}5\text{-}7\text{-}8}$, and by analysis of the ventricular gradients it was determined that primary T wave changes were produced in 5 of 6 normals, 4 of 11 patients with left ventricular hypertrophy, 5 of 7 with old anterior myocardial infarcts, and 4 of 7 with old posterior infarcts; the T wave changes showed a pattern that denoted delay of the repolarization of the posterior (diaphragmatic)-lateral aspect of the heart (Dowling and Hellerstein[2]). Balloon distention of the esophagus in 19 patients who had documented angina pectoris, and in whom electrocardiograms (Leads I, II, III, V_4) were taken, had only in one instance a 2-mm. depression of the S-T segment in Leads I and V_4 (with the balloon distention, pain and cardiac pain not being the same) while in 18 instances there was no change in the electrocardiographic pattern (Kramer and Hollander[4]).

2. IN ANIMALS. *In frogs.* Warming of the heart by radiation: If the T deflection is positive (that is, in the same direction as the initial deflection) the effect of warming the apical Lead is to render the T deflection more strongly positive; if the T deflection is negative, it is easily rendered positive by warming the apex; conversely, by warming the base of the ventricle, a positive T deflection can be rendered negative, or a negative variation rendered more strongly negative (Mines[5]).

In dogs: Distention of the esophagus by a glass tube with a thickened end results in a drop in arterial blood pressure (Tournade and Rocchisani[7]). Balloon distention of the lower esophagus resulted in an increase in coronary blood flow, regardless of changes in blood pressure (Hinrichsen and Ivy[3]).

Many factors may initiate myocardial infarction. It is usually assumed, and probably rightfully so, that these factors act in the presence of preexisting obstructive coronary artery disease. However, myocardial infarction may and does occur when there is no postmortem evidence of an obstruction for the blood flow in the coronary arteries. Spastic constriction has been one of the clinical postulates. Recent experiences in coronary arteriography would seem to have demonstrated the visibility of constriction and dilatation of the coronary vessels, in man (Arnulf[1]) and in dogs (West and Guzman[8]).

Whether in our own 4 cases one should consider a reflex effect on the heart, or actually induced temperature changes of the heart by contiguity, remains irrelevant for clinical purposes.

We have observed further instances where, subsequent to an acute myocardial infarction, drinking of ice-water induced recurrence of anginal distress.

If our observations are supported by others, the precautionary avoidance of very cold fluid and very hot food intake may be considered.

Summary. Deglutition of ice-cold drinks in 3 instances, and lodging of a hot food bolus in one instance, initiated myocardial infarction. In none of these patients did the anginal syndrome pre-exist.

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SUMMARIO IN INTERLINGUA

Infarcimento Myocardial per Reflexo Esophagic

Infarcimento myocardial esseva initiate in 3 casos per le deglutition de bibitas glaciate e in un caso per le stationamento de un bolo de alimento calide in le esophago. Nulle de iste patientes habeva ulle pre-existente syndrome anginal.

SUMMARIO IN INTERLINGUA

(See page 197 for original article)

Toxicitate Comportamental de Emylcamato (Striatrano)

Le effectos de doses solitari de 800 mg de emylcamato, 400 mg de emylcamato, 800 mg de meprobamato, e de correspondente placebos esseva studiate con respecto a lor toxicitate comportamental in un batteria de 18 variabiles. Quaranta-novem normal subjectos mascule esseva pre-trainate e testate sub omne le 4 formas de tractamento secundo un schema bis-occulte e contra-balanciate in que omne subjecto esseva su proprie subjecto de controlo.

Esseva effectuate, in tests de conduction automobilari, septe determinationes del tempore de reaction, del accuratia, e del preferimento in le selection del velocitate. Octo mesurationes del functiones visual esseva effectuate con le instrumento "Ortho-rater" de Bausch e Lomb. Le stabilitate manual esseva testate in tres probas con le planca de stabilitate de Whipple. In comparation con le resultatos obtenite con placebos, 800 mg de emylcamato—un dosage ben superior al recommendate quantitate pro solitari administrationes clinic—produceva un significative relentamento del tempores de reaction, durante que 400 mg de emylcamato non produceva ulle tal effecto. Ni le un ni le altere dosage exerceva un effecto uniforme super le accuratia, e 400 mg de emylcamato augmentava le cautitate del subjecto in sacrificar velocitate in favor de accuratia. Doses de 800 mg de meprobamato—duo vices le usual dosage clinic e grossiermente equivalente, in effectos clinic, con 400 mg de emylcamato—resultava tanto in un relentamento del tempore de reaction como etiam in un reduction del accuratia. Doses de 800 mg del un e del altere droga pareva exercer un effecto super componentes del comportamento psychomotori que es relationate al conducer un automobile. In le caso de emylcamato iste effecto concerneva primarimente le tempore de reaction. In le caso de meprobamato le effecto esseva minus specific e afficeva tanto le reaction e etiam le accuratia.

Es presentate explicationes de iste apparente incongruentia inter le presente constatationes relative a meprobamato e le resultatos de previe studios. Nulle toxicitate comportamental esseva detegite per nostre tests pro dosages de meprobamato de minus que 800 mg. Le dose clinic pro administrationes unic es usualmente 400 mg.

THE DIGITAL RHEOPLETHYSMOGRAM DURING ASIAN INFLUENZA*

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A major objective of the multidisciplined investigation of epidemic influenza (Type A, Asian strain) was the elucidation of the qualitative and quantitative alterations in peripheral circulation attributable to the influenzal infection (Burch, Walsh and Mogabgab[6], Walsh *et al.*[8]). In addition to basic data relative to physiological response to infection, it was hoped that some of the mechanisms of the clinical cardiovascular complications of influenza could be discovered. Digital rheoplethysmography was used to investigate the peripheral circulatory manifestations of Asian influenza since it is an extremely sensitive method for recording, simultaneously, continuous curves of the time course of volumes, rates, and accelerations in inflow, outflow, and differences between inflow and outflow in the digit during a single pulse cycle. Such a study could help to elucidate some of the vasomotor phenomena well known in influenza.

Materials and Methods. Multiple digital rheoplethysmographic recordings were made on 20 subjects during the course of infection with Asian influenza. In 16 of these patients the diagnosis of influenza was confirmed by serial hemagglutination studies or isolation of the virus. These patients were free from cardiovascular or circulatory disease. Recordings were made for the right index fingertip at the height of the patient's illness, during convalescence, and several weeks later, after full recovery. All recordings were made while the patients were resting in a hospital bed in a room with controlled atmospheric temperature and humidity (78° F., 46% relative humidity). The arm and hand were passively supported, with the fingertip at heart level. Total digital volume, digital bone volume, soft tissue volume, average resting volume of blood contained within the digital vascular bed, and digital surface area were calculated by methods previously described (Burch[2,3]). Circulatory responses to stimuli, including the ringing of a bell and deep inspiration, were recorded. The rheoplethysmograms were analyzed by methods previously described (Burch[2,3]).

Results. Typical rheoplethysmograms are shown in Figs. 1, 2, and 3. I_v, O_v, and D_v represent respectively, time course curves of the volumes of inflow, outflow, and the differences between these 2 volumes. I_R, O_R, and D_R represent respectively, the time course curves of the rates of inflow, outflow, and the difference between these 2 rates. The second right finger was used in all determinations.

In 15 patients this type of rheoplethysmogram was obtained during the height of illness, with subsequent return to normal during convalescence and recovery. The degree of digital vasoconstriction varied considerably among the members of this group, generally paralleling the severity of illness at the time of observation. Responses to stimuli (bell and deep inspiration)

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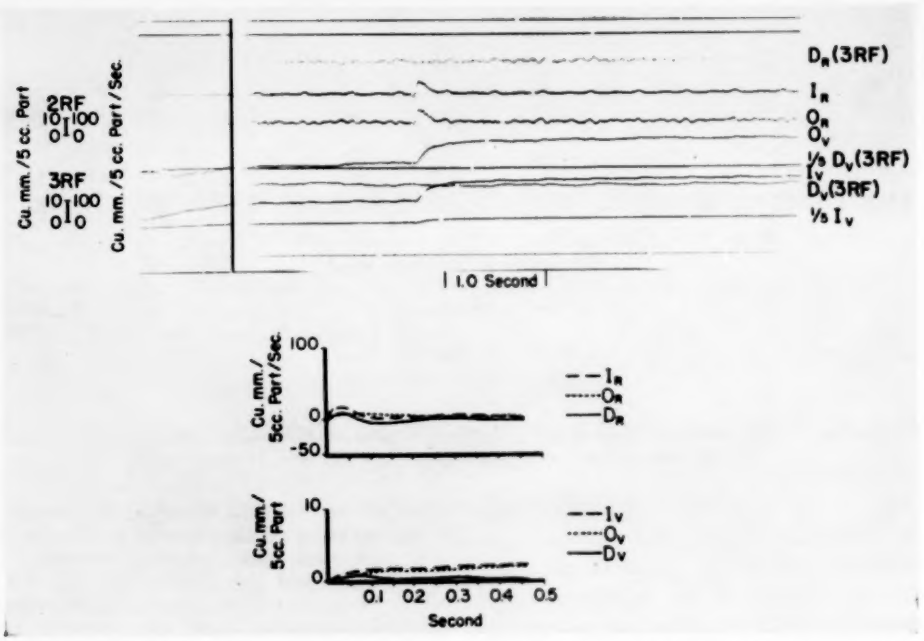

Fig. 1.—Rheoplethysmogram of right index finger (2RF) and right middle finger (3RF), recorded simultaneously during the height of Asian influenza. I_R, O_R and D_R represent rates of inflow, outflow, and difference between these 2 values for the right index finger. I_V, O_V and D_V represent volumes of inflow, outflow, and difference between these 2 volumes for the right index finger. The D_V and D_R for the right middle finger are included. The upper tracings are actual recordings, the lower consist in enlarged rate and volume curves for a single pulse cycle. These findings are indicative of digital vasoconstriction.

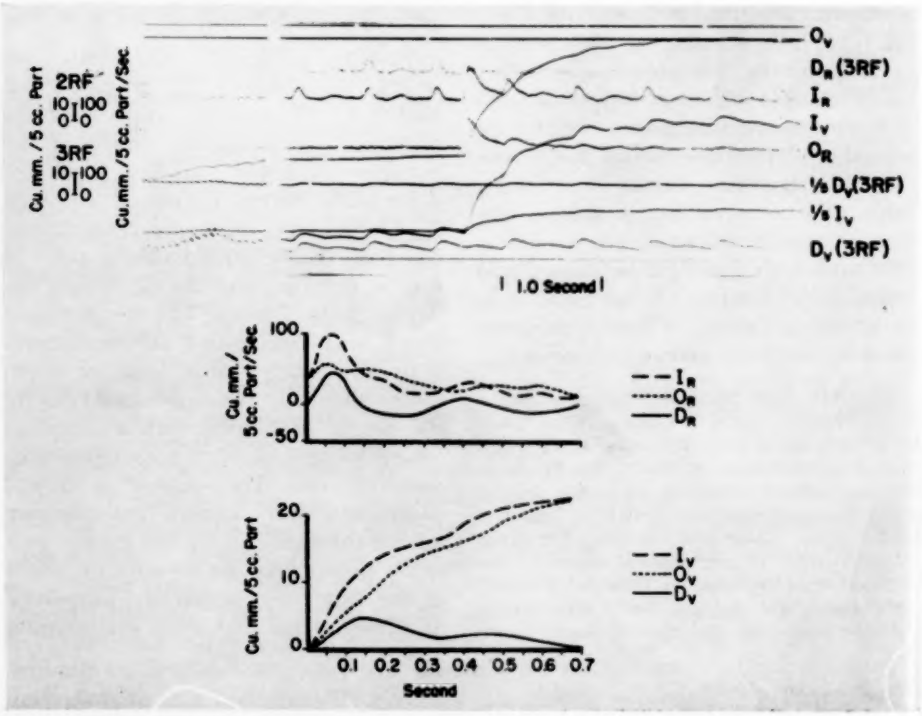

Fig. 2.—Rheoplethysmogram of the same patient taken during convalescence from Asian influenza. The lower series of curves show a considerable diminution in vascular constriction.

were normal, although proportionately of reduced magnitude at the time of digital vasoconstriction, as were the magnitudes of the pulse wave and of the alpha and beta deflections.

Study of the data presented in Tables 1 and 2 reveals that almost invariably, total digital inflow volume per pulse ample, subject 5, during the acute phase of influenzal infection, required almost 35½ minutes to effect turnover of total digital volume at mean rate of flow, but less than 3½ minutes for the same phenomenon after he had recovered from the influenzal infection. In those patients who exhibited a more

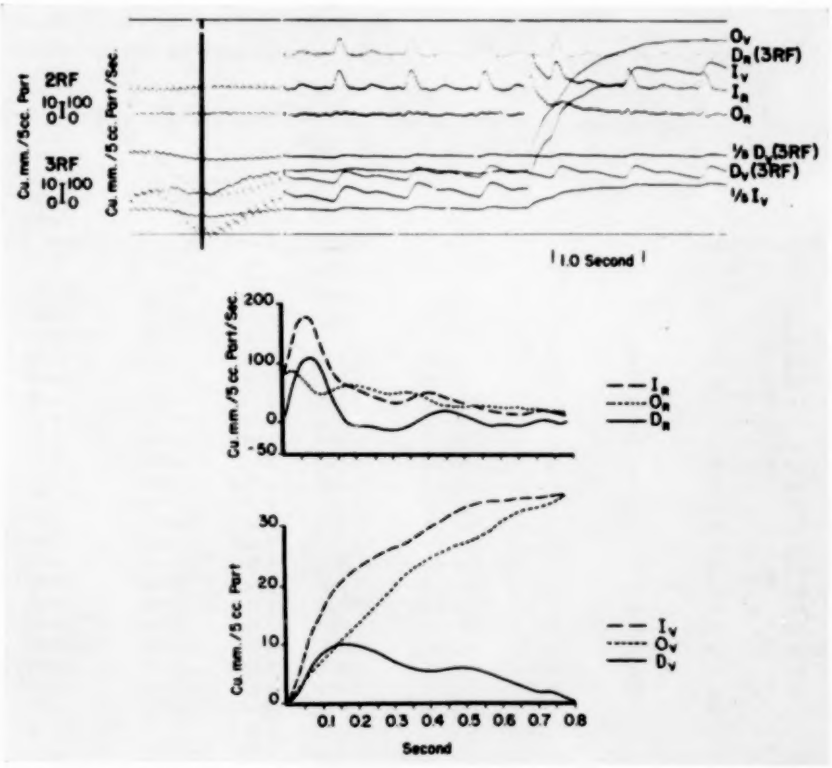

Fig. 3.—Rheoplethysmogram of the same patient taken after recovery from Asian influenza. Digital vascular tone has returned to normal.

cycle was less than 0.7% of the total digital volume, although there are considerable differences during various stages of illness in the same patient. A more obvious presentation of the individual's response to illness is the comparison of the time required for inflow volume at the mean rate of flow to equal total digital volume. For example, subject 5, during the acute phase of influenzal infection, required almost 35½ minutes to effect turnover of total digital volume at mean rate of flow, but less than 3½ minutes for the same phenomenon after he had recovered from the influenzal infection. In those patients who exhibited a more rapid digital turnover rate during the height of illness than during convalescence, recovery, or both, the quantitative differences between stages of illness were of much less magnitude than in those patients in whom reduced digital flow occurred at the height of illness. Moreover, these "increased" turnover rates noted during the acute

stage of the influenzal infection were within normal limits.

To estimate further circulatory status, the time course of inflow remaining as percentage of blood flowing in at any moment in the pulse cycle was determined at .05 second intervals from the formula:

$$\frac{I_{Vt}-O_{Vt}}{I_{Vt}} \times 100 = \frac{D_{Vt}}{I_{Vt}} \times 100$$

but never reached 100%. This is in contrast to the 100% retention routinely noted in normal subjects on exposure to cold or in patients with low diastolic blood pressure. In the latter instance retention may be attributed to the critical opening and closing phenomena of Burton. The complete absence of clinical cardiac disease in these patients implicates peripheral mechanisms, specifically constriction of the arterioles and

TABLE 1.—COMPARISON OF DIGITAL VOLUME OF FINGER TIP, SOFT TISSUE, AND BONE IN 20 SUBJECTS

Subject No.	*Age (Yr.)*	*Sex*	*Color*	*Blood Pressure*	*Digital Volume*			*Surface Area of Finger Tip ($cm.^2$)*
					Finger (ml.)	*Soft Tissue (ml.)*	*Bone*	
1	35	F	C	130/85	3.910	3.336	0.574	10.45
2	29	F	W	120/60	4.220	3.587	0.633	10.98
3	20	M	C	130/76	5.550	4.666	0.884	13.26
4	33	F	C	140/80	4.380	3.717	0.663	11.26
5	21	M	W	110/70	4.190	3.563	0.627	10.93
6	18	M	C	102/56	4.510	3.822	0.688	11.48
7	17	F	C	108/58	2.950	2.169	0.781	8.81
8	12	M	C	110/70	2.160	1.916	0.244	7.46
9	43	F	W	124/72	3.640	3.117	0.523	9.99
10	22	F	C	112/62	4.790	4.049	0.741	11.96
11	19	F	C	110/78	3.760	3.214	0.546	10.19
12	29	F	C	116/64	3.650	3.125	0.525	10.01
13	23	F	C	110/78	4.150	3.530	0.620	10.86
14	37	F	C	126/62	3.080	2.662	0.418	9.03
15	30	F	C	144/108	3.570	3.060	0.510	9.87
16	34	M	C	156/76	6.310	5.282	1.028	14.56
17	31	F	C	130/62	2.660	2.322	0.338	8.31
18	20	M	W	100/50	3.590	3.076	0.514	9.90
19	27	F	W	96/54	3.050	2.638	0.412	8.98
20	24	M	W	140/76	4.800	4.057	0.743	11.97
Mean	26	—	—	121/70	3.946	3.345	0.601	10.51

where I_{Vt} and O_{Vt} represent the accumulated volume of inflow and outflow respectively, in c.mm. per 5 ml. of part at time t.

It was found that in those patients who exhibited vasoconstriction, the percentage of inflow remaining at any one time during the pulse cycle was greater during the period of vasoconstriction (height of illness) than during subsequent periods. The degree of lag in outflow volume was proportional to the degree of vasoconstriction, the vessels of the arteriovenous shunts. Outflow lag was not noted in any patient who did not exhibit vasoconstriction.

Discussion. The extreme reactivity of the digital circulation has been long recognized. Similarly appreciated has been the high rate of digital blood flow which, under comfortable environmental circumstances, approximates that of the liver, brain, and left ventricular myocardium (Burch[4]). Thermal regulation, tissue repair, nutrition,

TABLE 2.—"TURNOVER" OF INFLOW IN DIGIT DURING PULSE CYCLE

Subject No.	Clinical State	Vol. Inflow Per Pulse Cycle (c.mm./5 ml. part)	Vol. Inflow Per Pulse Cycle (% vol. digit)	Mean Rate of Inflow (c. mm./5 ml. part/sec.)	Time of "Turnover" for Mean Rate (I_V = Vol. Finger Tip)* (sec.)
1	Acute	13.5	0.27	22.5	221.6
	Conv.	—	—	—	—
	Recov.	11.0	0.21	11.0	454.7
2	Acute	11.8	0.24	16.4	304.9
	Conv.	21.2	0.42	31.6	158.2
	Recov.	14.5	0.28	20.1	248.7
3	Acute	6.5	0.13	10.8	462.9
	Conv.	10.0	0.16	13.3	459.0
	Recov.	23.0	0.37	27.1	210.2
4	Acute	7.2	0.14	13.6	367.6
	Conv.	11.0	0.22	14.7	324.6
	Recov.	21.0	0.42	24.7	202.1
5	Acute	1.8	0.04	2.3	2122.0
	Conv.	—	—	—	—
	Recov.	26.2	0.52	26.7	187.2
6	Acute	8.2	0.16	13.7	397.1
	Conv.	10.5	0.21	10.5	477.2
	Recov.	13.3	0.26	11.6	438.6
7	Acute	4.8	0.09	6.4	480.1
	Conv.	28.5	0.57	25.9	110.6
	Recov.	—	—	—	—
8	Acute	7.0	0.14	12.7	395.5
	Conv.	16.0	0.32	22.5	223.3
	Recov.	28.5	0.57	39.6	126.8
9	Acute	25.0	0.50	37.3	134.1
	Conv.	—	—	—	—
	Recov.	36.2	0.72	47.6	102.1
10	Acute	3.7	0.07	7.4	703.8
	Conv.	23.5	0.47	29.4	166.5
	Recov.	37.0	0.64	48.7	102.6
11	Acute	5.5	0.11	10.0	500.0
	Conv.	24.2	0.48	34.6	144.5
	Recov.	30.0	0.60	31.6	158.2
12	Acute	6.5	0.13	13.0	384.6
	Conv.	23.5	0.47	33.6	108.0
	Recov.	22.0	0.43	25.3	143.5
13	Acute	30.2	0.60	39.7	125.9
	Conv.	26.5	0.53	33.3	150.1
	Recov.	35.0	0.70	33.3	150.1
14	Acute	22.0	0.41	40.0	125.0
	Conv.	22.2	0.44	31.7	157.7
	Recov.	26.5	0.53	37.9	131.8
15	Acute	5.3	0.11	10.0	500.0
	Conv.	18.7	0.37	28.8	173.5
	Recov.	2.5	0.05	37.8	132.3
16	Acute	5.3	0.10	9.6	520.8
	Conv.	4.1	0.08	7.5	666.6
	Recov.	12.7	0.25	19.2	260.4
17	Acute	29.5	0.59	53.6	93.3
	Conv.	15.8	0.24	24.3	205.7
	Recov.	17.5	0.35	19.4	257.7
18	Acute	32.7	0.65	59.5	84.1
	Conv.	28.8	0.57	33.9	147.7
	Recov.	24.7	0.48	35.3	141.6
19	Acute	51.6	1.03	73.7	67.8
	Conv.	50.5	1.01	67.3	74.3
	Recov.	—	—	—	—
20	Acute	2.3	0.04	50.0	100.0
	Conv.	22.5	0.45	22.1	226.2
	Recov.	35.5	0.71	44.4	112.6
Mean	Acute	14.0	0.28	25.1	404.6
	Conv.	21.0	0.41	27.4	233.7
	Recov.	23.2	0.45	30.1	197.8

*Time in seconds for the inflow volume, at the mean rate of flow, to equal the volume of the finger tip.

and the sustenance of tactile sensory function are the principal activities which the digital blood supply must support. The relative demands of each of these on digital blood flow are unknown. Certainly the early appearance of paresthesias of the fingertips during exposure to cold indicates the sensitivity of tactile sensation to reduction in digital blood flow and suggests that this function is the most sensitive of those mentioned.

While the vasoconstriction of exposure to cold must be a facet of body heat conservation, the vasoconstriction of influenzal infection, manifested during a period of increased body temperature, would not seem to serve the same purposes. Probably the usual compensatory mechanisms of temperature control had not yet been evolved at the time of rheoplethysmography. Thus the vasoconstriction observed could have been merely a manifestation of the precompensatory phase of fever production. If this is so, similar studies obtained only a short time later would have revealed the vasodilatory response eventually effected by sufficient stimulation of the heat regulatory center. Perhaps such vasoconstriction is a response to the stress of infection, as are similar vascular changes noted during stimulation with a bell, psychic trauma, or norepinephrine. In view of the disproportionate tachycardia and bradycardia commonly found in influenzal infection, it is possible that these phenomena, in conjunction with vasoconstriction are a manifestation of dysfunction of the autonomic nervous system. In this connection it is interesting to note that in spite of the intense vasoconstriction exhibited by many of these influenzal patients, no instance of the "hunting phenomenon" described by Lewis was encountered. The latter represents a normal response to continued exposure to cold. The periodic increments in digital blood supply teleologically represent attempts at tissue survival, whatever the physiological basis. The absence of the "hunting phenomenon" would suggest that the degree of vasoconstriction encountered in influenzal infections is limited. These studies substantiate this. Finally, one can not dismiss the possibility that the vascular reaction was at least in part mediated through cells of the chromaffin type. The latter have been demonstrated in the human digital corium, particularly concentrated around blood vessels, nerves, and sweat and sebaceous glands (Adams-Ray and Nordenstam[1-3], Burch and Phillips[5]). These cells could act either as mediators of a more central stimulus, or as purely peripheral phenomena evolved by local alterations in tissue metabolism or perfusion.

A direct consequence of the marked peripheral vasoconstriction encountered in these influenzal patients is the shift of a considerable portion of the intravascular fluid volume to deeper structures. This may represent hemometakinesia, that is, the physiological process whereby blood is shunted from less vital to more essential areas during times of need. It most certainly represents a considerable increase in amount of blood shifted to the lungs. Such an increment in pulmonary blood volume could be of significance in the presence of reduced cardiac reserve, even to the point of precipitating pulmonary congestion and edema. The latter have been noted in patients with influenzal infections complicating underlying cardiac disease. To this must be added the direct injury to the myocardium and blood vessels which may follow influenzal infection, as well as the pulmonary infection which interferes with the pulmonary circulation.

Consideration must also be given to the increased cardiac work associated

with the systolic accentuation of inflow acceleration exhibited by so many of these patients. Although brief in duration, it represents still another burden imposed upon the heart by the influenzal infection.

Summary. Rheoplethysmography of 20 patients with Asian influenza revealed peripheral vasoconstriction and reduced digital flow at the height of illness in 15 patients. The configuration of the volume and rate curves was essentially normal as were the responses to deep inspiration and the sound of a bell, although of reduced magnitude in presence of constricted vessels. Four patients exhibited no change in digital flow with illness, whereas one evidenced definite increased flow. Accentuation of the dicrotic notch of the Dv curves was noted in approximately half of the patients and tended to disappear with recovery. This phenomenon occurred regardless of the state of vascular tone, and was associated with exaggeration of inflow acceleration early in systole.

Of the 5 patients who did not experience vasoconstriction, 4 showed no alteration in digital blood flow at any stage of observation. The fifth patient showed increased digital blood flow at the height of illness, with subsequent return to normal with recovery. It was interesting to note that this patient was the most seriously ill of the group and suffered from a complicating staphylococcic pneumonia. He was also the sole patient to exhibit hypotension, which was most marked at the height of illness.

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SUMMARIO IN INTERLINGUA

Le Rheoplethysmogramma Digital Durante Influenza Asiatic

Rheoplethysmographia de 20 patientes con influenza asiatic reveleva in 15 de illes un vasoconstriction peripheric e un reducite fluxo digital al culmine del morbo. Le configuration del curvas de volumine e intensitate esseva essentialmente normal; esseva etiam normal le responsas a inspiration profunde e al sono de un campana, ben que le magnitude de illos esseva reducite in le presentia de vasos constringite. In quatro patientes le morbo esseva accompaniate per nulle alterationes in le fluxo digital, durante que in un patiente le fluxo esseva definitemente augmentate. Un accentuation del incision dicrotic del curvas Dv (= differentia inter volumine de influxo e volumine de effluxo) esseva notate in approximativemente un medietate del patientes. Illo tendeva a disparer con le recuperation del patiente. Iste phenomeno occurreva sin reguardo al stato del tono vascular e esseva associate con un exaggerate acceleration del influxo in le prime parte del systole.

Inter le 5 patientes qui non exhibiva vasoconstriction, 4 monstrava nulle alteration del fluxo sanguinee digital a ulle stadio de observation. Le quinte patiente exhibiva un elevate fluxo de sanguine digital al culmine del morbo e retorno a un nivello normal con le recuperation. Il es notabile que iste patiente esseva le plus gravemente malade del gruppo e que ille suffreva le complication de un pneumonia staphylococcic. Ille esseva etiam le sol patiente qui exhibiva hypotension, le qual esseva le plus marcate al culmine de su morbo.

SUMMARIO IN INTERLINGUA

(See page 186 for original article)

Le Relation Inter Diabete Mellite e Infectiones del Vias Urinari

Specimens de urina ab 300 diabeticos e 200 patientes de controlo esseva analysate pro proteinuria, pyuria, e numeration bacterial.

1. Grados significative de bacteriuria esseva constatate in 6% del patientes con diabete. Isto non differe marcatemente ab le resultatos obtenite per altere autores in le population normal.

2. Le numeration de bacterios vive in le urina de patientes con diabete esseva plus alte que illo observate in le patientes de controlo sed non attingeva valores pathologic.

3. Le curva del numerationes bacterial in "ben stabilisate" diabeticos esseva simile al curva correspondente in le patientes de controlo. Le curva in "mal stabilisate" diabeticos esseva proxime a valores pathologic.

4. In casos de infection active, *Escherichia coli* esseva le organismo isolate le plus frequentemente. In le basse numerationes bacterial in le subjectos de controlo e le non-inficite diabeticos, coccos positive al Gram predominava.

5. Similissime numerationes bacterial esseva observate in specimens ab patientes tractate exclusivemente per restrictiones dietari e in illos ab patientes tractate (intermittentemente) con carbutamido o con insulina.

6. In un gruppo de 22 patientes con syndrome de Kimmelstiel-Wilson, 13 habeva urinas sterile. In le alteres, in qui contamination esseva presente, le numeration bacterial esseva plus proxime a illo del subjectos de controlo que a illo del altere diabeticos.

Super le base de iste constatationes, le these es presentate que le notion traditional que infection del vias urinari es plus frequente in patientes con diabete que in alteres deberea esser revisionate. Nonobstante, il pare esser correcte que le vias urinari de patientes con diabete, e specialmente de patientes feminin, es plus susceptibile de esser inficite per bacterios. Le stabilisation routinari del diabete de tal patientes preveni le disveloppamento in illes de infectiones active.

OBSERVATIONS ON THE EPIDEMIOLOGY OF STAPHYLOCOCCAL INFECTIONS

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In an earlier communication, the experience of Temple University Medical Center with coagulase-positive staphylococcal infections was reported for the year 1956 (Schreck *et al.*[8]). The hospital's Committee on Infections considered certain measures (Caswell *et al.*[3]) to be important in the control of these infections and accordingly attempted to bring such measures into practice. Since 1956, this study has been a continuing one made on a prospective rather than a retrospective basis. The composition and function of the committee has already been recorded (Schreck[9]). The purpose of the present report is to put forth certain information relative to the natural history or epidemiology of coagulase-positive staphylococcal infections which can be provided only by medical microbiology and is therefore independent of the function of the usual Infections Committee. The points concerning epidemiology in this paper were derived from a 4-year period 1956 through 1959.

Methods and Materials. RECORDS. As indicated elsewhere (Schreck[9]), the names of all patients from whom bacteriologic specimens have grown coagulase-positive staphylococci are reported to the committee. This report is submitted once a week and is the starting point for the committee to decide which patients have a true infection. A master index of all these names is kept in the author's laboratory. This index prevents a patient's name from being entered in the records more than once and also serves as the source for tabulation of all data. For each name on the master index, there is maintained a separate file sheet on which is entered all information concerning cultures subsequent to the original one. Thus the committee is concerned with the patient only once for the original classification of his infection status; but the patient's cultures remain under continuous scrutiny by the author regardless of when his first culture was obtained. On some patients' records, there are entries of cultural data for as long as 4 years.

CULTURES. The method of collection and culturing of specimens was routine as previously stated (Schreck *et al.*[8]). The performance of the tube coagulase test was also a standard procedure.

ANTIBIOTIC TESTING. Test tube antibiotic susceptibility tests were used to determine the antibiogram of the various strains of staphylococci. In these tests, 0.5 ml. of a 1:1000 dilution of an overnight broth culture of the staphylococcus was added to 0.5 ml. of nutrient broth containing 1, 10 and 100 units or micrograms of the appropriate antibiotic. All tests were incubated overnight at 37° C. and gross turbidity in any tube indicated resistance to that amount of antibiotic. In addition, the tests with penicillin 152 (Syncillin)* were read again after 48-hours incubation.

BACTERIOPHAGE PROPAGATION AND TYPING. Original samples of all phages used in this study were kindly furnished by Dr. John Blair of New York City. The typing set of phages was modified during the study in accordance with current recommendations (Committee Report[4]) and included the phages indicated in Table 1.

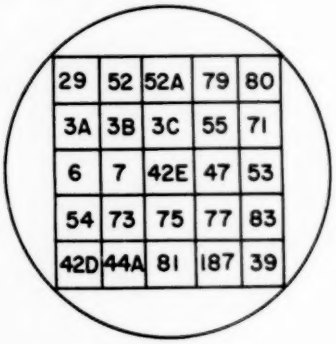
Propagation of phages and typing was initially conducted in the manner of Blair

*Generously furnished by Howard Albright, M.D., Bristol Laboratories, Inc., Syracuse, N.Y.

and Carr[1]. But for over 2 years, propagation has been performed at 4-month intervals in 200 ml. of trypticase soy broth containing the overnight growth from 2 agar slants of the propagating strain and 5 ml. of the undiluted phage. Such preparations were shaken on a rotary shaker for 4 hours at 30° C. The fluid was then passed through Seitz filters and prepared in 10-fold serial dilutions to determine the routine test dilution (RTD). This shaker method produces titers of phage comparable to those obtained by the plate method with rare exception.

TABLE 1

BACTERIOPHAGES USED IN TYPING



The actual typing was performed on trypticase soy agar plates to which calcium was added for a concentration of 0.1% as previously recommended (Rountree[6]). All 25 phages were added simultaneously to the swab-inoculated typing plates with a 25 pronged stamping plate of the author's design. If a strain of staphylococcus failed to react with any of the 25 phages at the RTD, it was again tested with 10^{-2} dilutions of all the phages. If a strain still failed to react, it was then called non-typable.

Results. HOSPITAL-ACQUIRED INFECTIONS RELATIVE TO PHAGE TYPES. Bacteriophage typing determines which strain of staphylococcus is infecting the patient. During the 4 years 1956 through 1959, the single predominant strain in our hospital-acquired infections continued to be the 80/81 type staphylococcus. Reference to Fig. 1 indicates that in the 4-year period 1060 individual patients acquired staphylococcal infections incident to their hospitalization. Since this number is substantial, it must be noted immediately that, when compared to the total number of admissions and births for the same period of time, the overall incidence of infection was only 1.1%. It will also be noted in Fig. 1 that during the first 3 years of the study 57% to 63% of the total infections were caused by the 80/81 staphylococcus; but in the fourth year, only 38% of the infections were caused by 80/81.

Figure 2 shows the yearly totals of major infections occurring postoperatively in clean surgical wounds. It too reveals a decrease in the fourth year of 80/81 infections. This tendency to disappearance of the 80/81 type was a finding common to all categories of hospital-acquired infections; that is, total surgical infections (Fig. 3), infections not related to a surgical procedure (Fig. 4), infections in newborn infants and breasts of postpartum mothers (Fig. 5). In addition, the same decrease of 80/81 etiology was noted

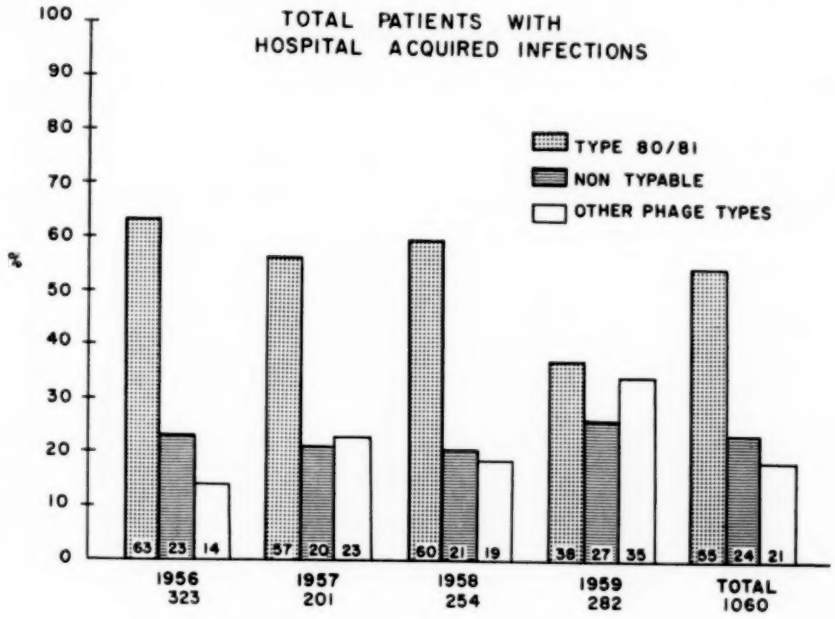

TOTAL PATIENTS WITH
HOSPITAL ACQUIRED INFECTIONS
TYPE 80/81
NON TYPABLE
OTHER PHAGE TYPES
%
100
90
80
70
60
50
40
30
20
10
0
63 23 14
57 20 23
60 21 19
36 27 35
55 24 21
1956
323
1957
201
1958
254
1959
282
TOTAL
1060

Fig. 1

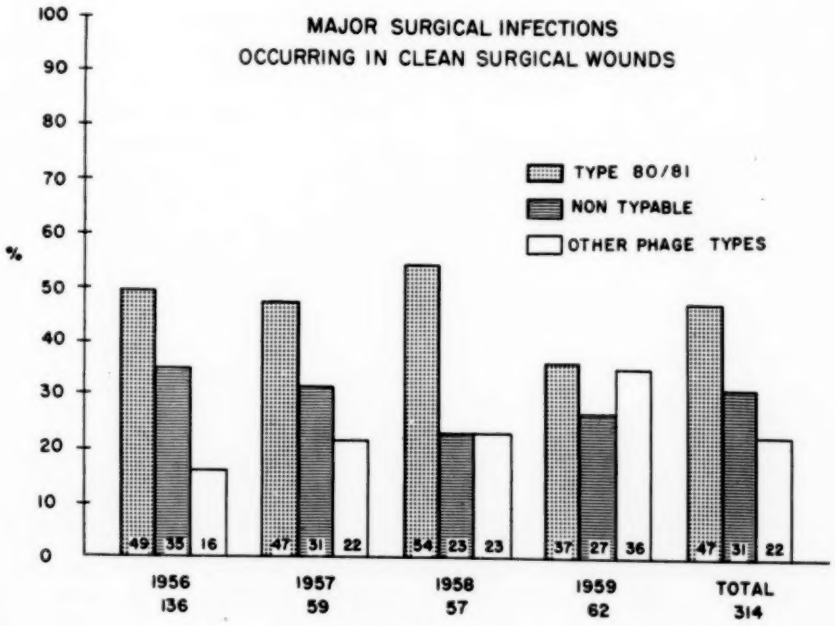

MAJOR SURGICAL INFECTIONS
OCCURRING IN CLEAN SURGICAL WOUNDS
TYPE 80/81
NON TYPABLE
OTHER PHAGE TYPES
%
100
90
80
70
60
50
40
30
20
10
0
49 35 16
47 31 22
54 23 23
37 27 36
47 31 22
1956
136
1957
59
1958
57
1959
62
TOTAL
314

Fig. 2

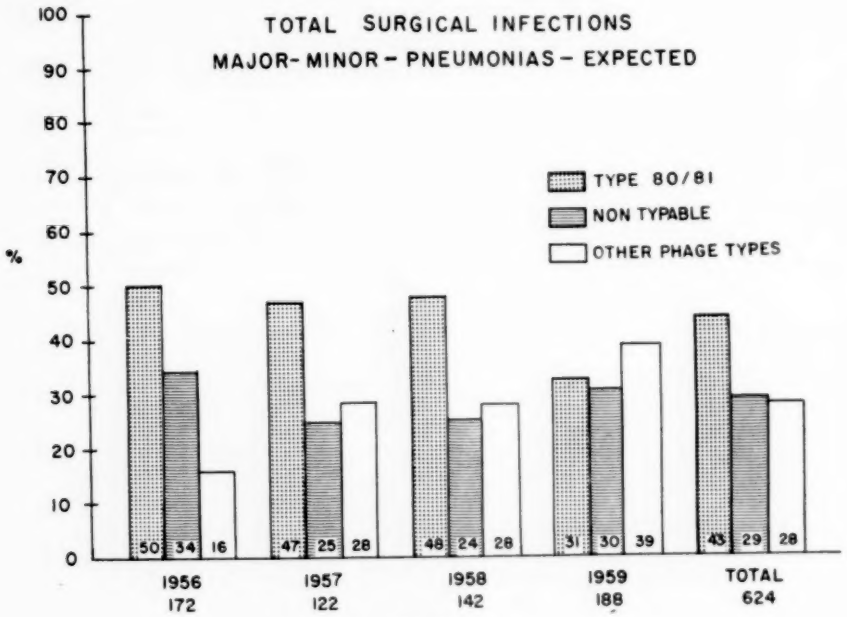

TOTAL SURGICAL INFECTIONS
MAJOR- MINOR - PNEUMONIAS - EXPECTED
TYPE 80/81
NON TYPABLE
OTHER PHAGE TYPES
%
100
90
80
70
60
50
40
30
20
10
0
50 34 16
47 25 28
48 24 28
31 30 39
43 29 28
1956
172
1957
122
1958
142
1959
188
TOTAL
624

Fig. 3

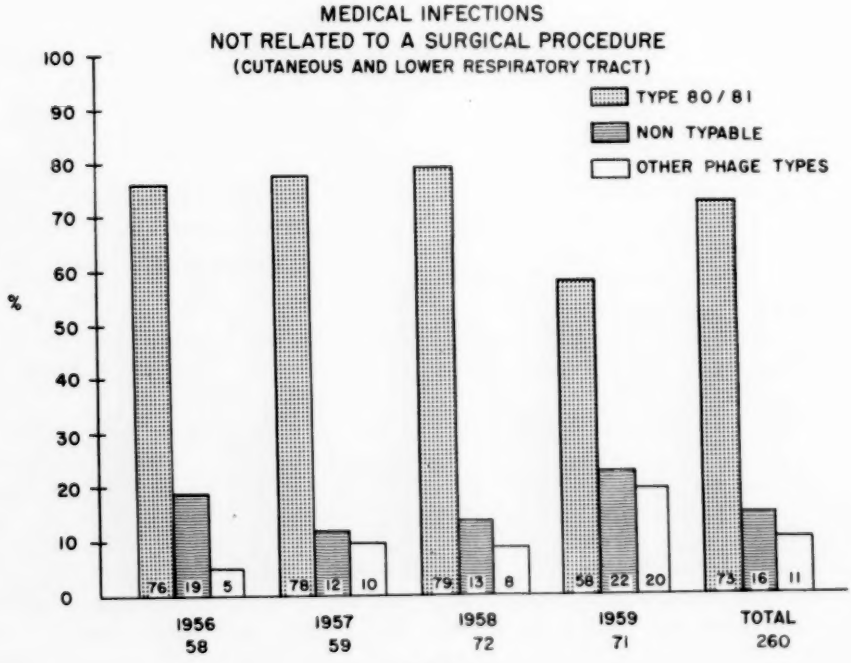

MEDICAL INFECTIONS
NOT RELATED TO A SURGICAL PROCEDURE
(CUTANEOUS AND LOWER RESPIRATORY TRACT)
TYPE 80/81
NON TYPABLE
OTHER PHAGE TYPES
%
100
90
80
70
60
50
40
30
20
10
0
76 19 5
78 12 10
79 13 8
58 22 20
73 16 11
1956
58
1957
59
1958
72
1959
71
TOTAL
260

Fig. 4

in hospital personnel infections in the fourth year (Fig. 6). But it should be noted that still in the fourth year 58% of the personnel infections and 58% of the medical infections (Fig. 4) were caused by the 80/81 type.

It may be noted in each category of infection considered above that the decrease in 80/81 etiology was offset by an increase of infections caused by other phage types. Therefore, attention was directed to the other phage types involved to learn if one particular type was replacing 80/81. Table 2 reveals other phage types that produced 2 or more infections in 1959. None of these occurred with great enough frequency to indicate that it

TABLE 2

OTHER PHAGE TYPES IN HOSPITAL ACQUIRED INFECTIONS-1959
(MOST COMMON OF 52 OTHER PHAGE TYPES)

7	11	47/53/75/77	2
77	9	3C	2
80	6	29	2
81	6	52A/7	2
7/77	4	29/52A	2
53	3	52/52A/80/81	2
3A	3	52/80	2
53/77/83	2	52/80/81	2
53/77	2	55/77	2

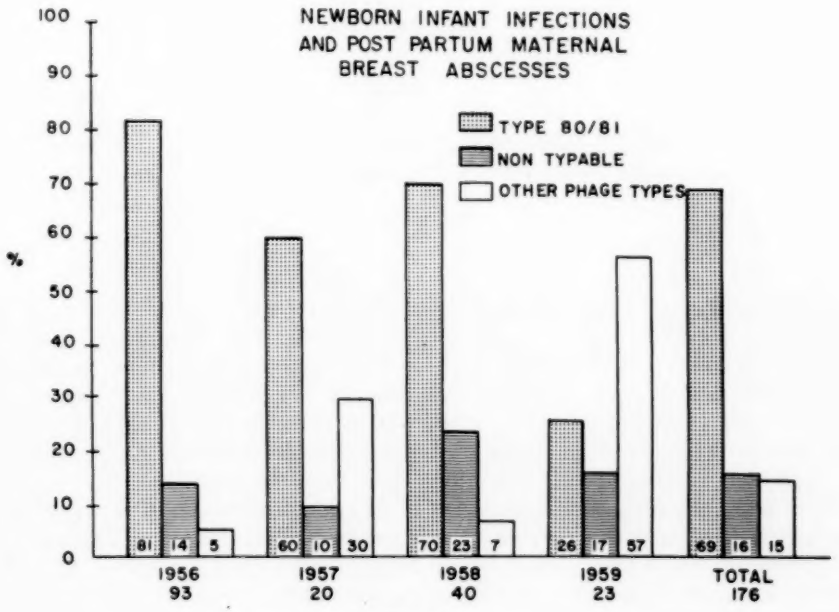


Fig. 5

was replacing 80/81; nor was any one of these considered to be a "newcomer" to the hospital environment.

PATIENTS ADMITTED WITH STAPHYLOCOCCAL INFECTIONS: NOT HOSPITAL RELATED. Figure 7 shows a progressive increase each year in the number of patients admitted to the hospital for treatment of an already existing staphylococcal infection. It should be noted that the number of these patients infected with the 80/81 type even before hospital contact varies between 16 to 30%. In 1959, 53% of these patients were infected with a typable organism other than the 80/81 type. The finding of 238 patients admitted with infection in 1959 does not necessarily mean an increase in staphylococcal infections in the community since undoubtedly some of this increase comes from patient referral to this institution.

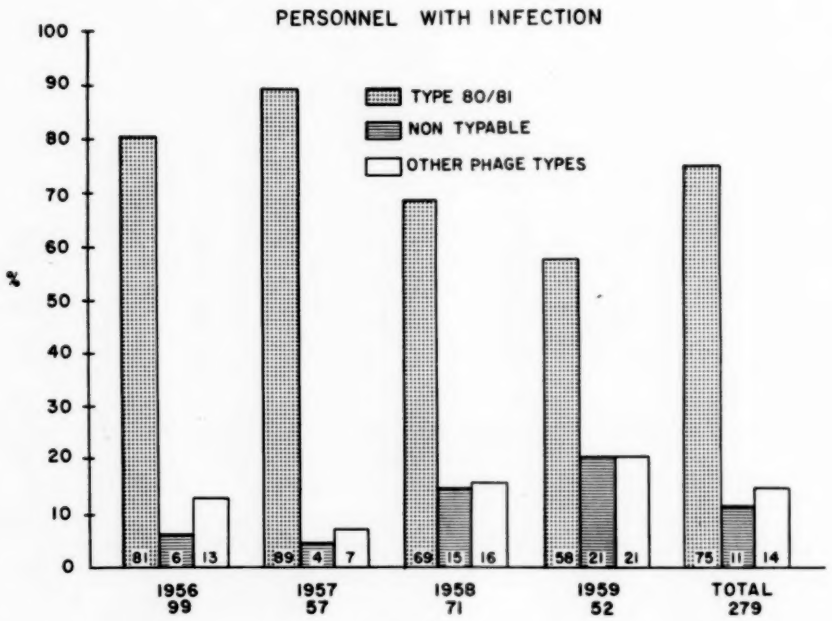


Fig. 6

CHANGE IN ANTIBIOGRAM. Test tube antibiotic susceptibility tests were performed in 1959 on 211 recently isolated strains from different patients to determine if any change in antibiogram had occurred since 1956. Recorded in Fig. 8 is the resistance demonstrated by the 80/81 strains, nontypable strains, and other phage types to 10 units or μg. of the various antibiotics tested. It is noted that in 1959, 80/81 was still resistant to penicillin, streptomycin, tetracycline and erythromycin. The other phage types were the least resistant and the non-typable staphylococci were slightly less resistant than the 80/81 type.

Figure 9 indicates the change in resistance which occurred between 1956 and 1959. Only changes of 10% or greater have been recorded. It is seen that there was a change toward sus-

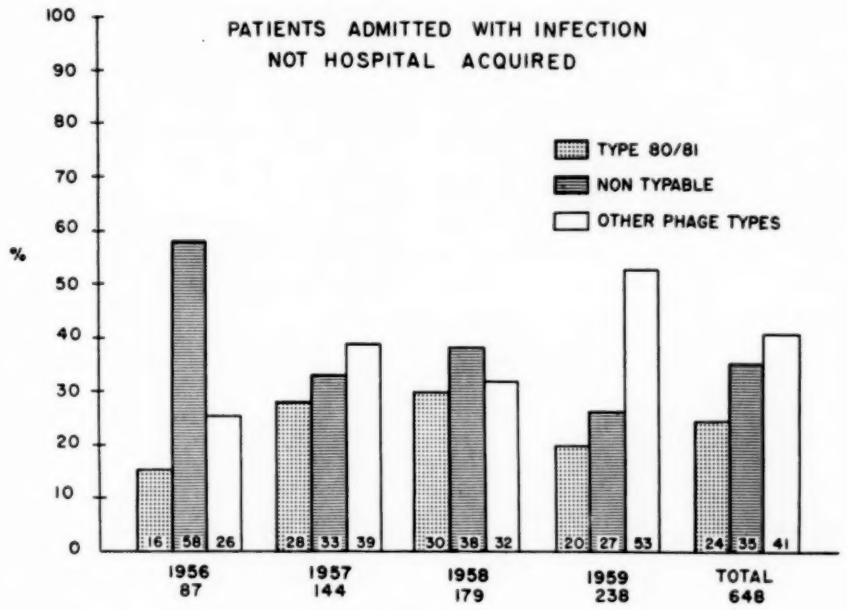

PATIENTS ADMITTED WITH INFECTION
NOT HOSPITAL ACQUIRED
TYPE 80/81
NON TYPABLE
OTHER PHAGE TYPES
%
100
90
80
70
60
50
40
30
20
10
0
16 58 26
28 33 39
30 38 32
20 27 53
24 35 41
1956
87
1957
144
1958
179
1959
238
TOTAL
648

Fig. 7

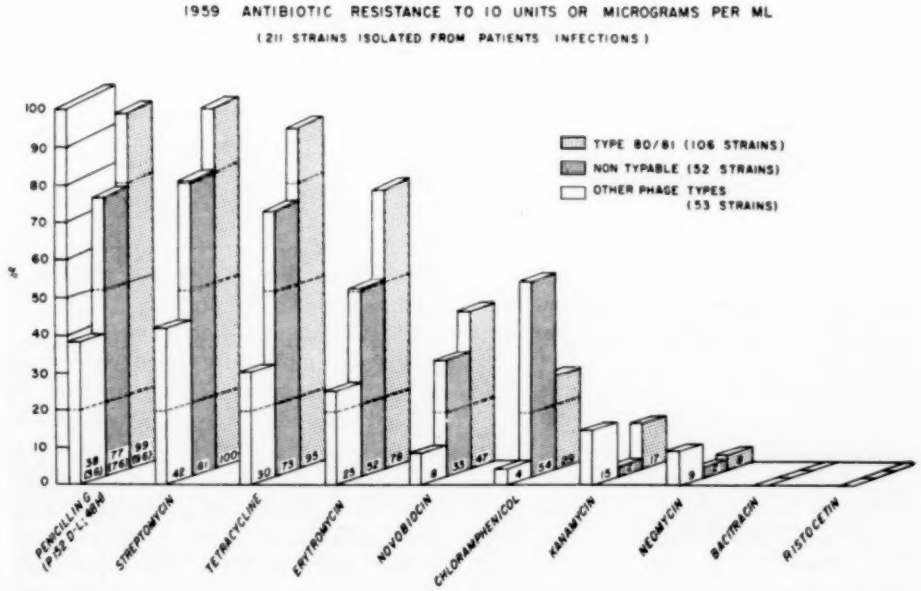

1959 ANTIBIOTIC RESISTANCE TO 10 UNITS OR MICROGRAMS PER ML
(211 STRAINS ISOLATED FROM PATIENTS INFECTIONS)
TYPE 80/81 (106 STRAINS)
NON TYPABLE (52 STRAINS)
OTHER PHAGE TYPES (53 STRAINS)
%
100
90
80
70
60
50
40
30
20
10
0
PENICILLIN G
STREPTOMYCIN
TETRACYCLINE
ERYTHROMYCIN
NOVOBIOCIN
CHLORAMPHENICOL
KANAMYCIN
NEOMYCIN
BACITRACIN
RISTOCETIN

Fig. 8

ceptibility: (1) to penicillin by other phage types, (2) to tetracycline by non-typable strains and other phage types, and (3) to erythromycin by type 80/81. There was a change toward resistance: (1) to novobiocin by 80/81 and non-typables, and (2) to chloramphenicol by type 80/81 and non-typable strains. It should be noted in Fig. 8 that a small percentage of staphylococci was resistant to kanamycin. Vancomycin was not tested in this series because of the uniform susceptibility of staphylococci to this antibiotic.

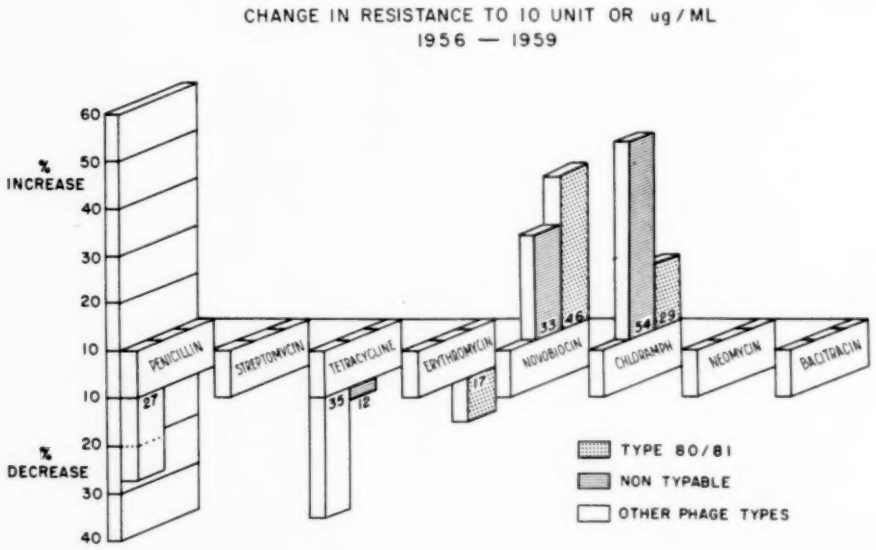


Fig. 9

Of special note in Fig. 8 is the fact that all strains exhibited resistance to penicillin 152 at 48 hours identical with the resistance to penicillin G at 18 hours. After 18 hours incubation in the tests with penicillin 152, 78% of the 80/81 strains were resistant to 10 units, 56% of non-typable strains were resistant, and 26% of the other phage types.

ENVIRONMENTAL RESERVOIR OF STAPHYLOCOCCI. Air studies with a sieve analyzer, summarized elsewhere (Schreck[9]) have shown that the air of this institution is not heavily burdened with staphylococci and in particular the 80/81 type. Blankets after a routine laundry process have also been found free of the 80/81 type even after coming from the bed of patients with such an infection (Schreck[9]). Sporadic checks of inanimate objects and floors throughout the hospital have rarely detected the 80/81 strain.

NASAL CARRIERS AMONG PERSONNEL. A search for nasal carriers of type 80/81 in the hospital personnel in 1956 revealed only 4% of 640 persons to be such carriers (Schreck *et al.*[8]). In 1959, 100 personnel working in the surgical suite were again examined and none was found to be a carrier of the organism. In addition, 55 nursery personnel were recently examined periodically; 6 nasal carriers of type 80/81 were found. Three of these were stu-

dent nurses and 3 were permanent personnel. Three of the 6 lost the organism spontaneously and 2 others resigned for other reasons.

PERSONNEL INFECTIONS. Figure 6 reveals the number of personnel who developed proven staphylococcal infections in each year of the study. These figures have been maintained in the same manner as the patient infection records; that is, a name is entered only once for the original culture. In 1959 there were only 52 of the personnel who developed their first staphylococcal infection; but, since several persons continued to have recurrence, there was a greater total number of infections in the personnel.

AGE AND DIABETES PREDISPOSING TO INFECTION. The age distribution of patients developing infections incident to hospitalization was determined for the first year of the study during which we experienced the greatest total number and incidence of infections. The data were adjusted to exclude newborn infants and maternal breast abscesses so that the bias of these 2 special groups would be removed. Figure 10 indicates the age distribution of 200 patients. It is noted that the peak distribution was in the decade 51 to 60.

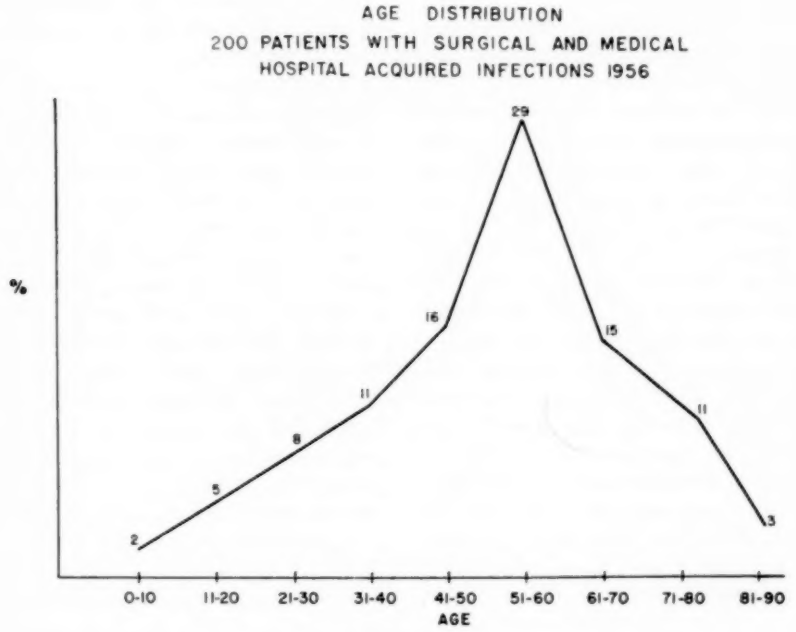


Fig. 10

Patients with diabetes mellitus admitted to the hospital free of staphylococcal infections constituted 4% of the total admissions for the 4 years. The incidence of hospital-acquired infection for these "clean" diabetics was 1.4% while the incidence in "clean" non-diabetic patients was 1.3%. In contrast, of the patients admitted to the hospital for therapy of an existing staphylococcal infection 12% were diabetics.

CHANGE OF PHAGE TYPE IN THE INFECTION. Without resort to a definite plan, multiple cultures were obtained from 270 patients with sufficient interval between cultures to ascertain if the original infecting staphylococcus was later replaced by a different phage type. In this group, there was clear evidence of change in only 3 instances. In 2 cases, the change was from a non-typable organism to the 80/81 type and in the third case the change was from 3B/39 to 80/81. In this same group of patients, examples of the longest persistence and recurrent infections were found in 11 patients who experienced recurrent infection from 7 to 48 months. In 10 of these patients the organism was 80/81 and in the eleventh it was non-typable.

BACTEREMIA AND PAROTITIS. Bacteremia was detected in 49 of the total hospital acquired infections for an incidence of 4%. No one phage type of staphylococcus had any greater propensity to cause bacteremia. The same rate of 4% bacteremia was noted in the patients who were admitted with established staphylococcal infections. Again in these patients there was no marked difference according to phage type. The categories in which bacteremia occurred most frequently were newborn infants and pneumonias (11 to 12%). Mortality rate should logically follow at this point, but, because of the difficulty of determining whether a patient died of his septicemia or because of his underlying neoplasia, myocardial infarct or whatever, fatality rates will not be considered in this study.

Only 6 patients were seen with parotitis of staphylococcal etiology. Five of these were hospital acquired and one was admitted from the outside. None was a postoperative complication.

Discussion. EFFECT OF CONTROL MEASURES. The foregoing results pertinent to the epidemiology of staphylococcal infections should have been influenced by the control measures which were recommended in 1956. The results must therefore be interpreted in part, at least, according to how well the control measures were actually put into practice. It is the opinion of the author that measures relative to changes in surgical procedure were well accepted and adhered to. Attempts at isolation of infected patients were not uniform and the curtailed use of prophylactic antibiotics was not effected. With the exception of the surgical suite, general housekeeping measures were the most difficult to standardize beyond general cleaning. Personnel who were healthy nasal carriers of the 80/81 type were not removed from duty nor was their removal ever recommended. Personnel with active infection were, however, relieved of duty and every effort was made to enforce this policy. In essence then, during the 4 years, there were no marked changes to influence the spread of the organisms with the exception of certain changes in surgical procedures (Caswell *et al.*[3]) and removal of infected personnel from duty.

Considering the yearly totals of hospital acquired infection in Fig. 1, it is seen that the fewest patients became infected in 1957. In the next 2 years there was a progressive increase but still not to the peak of 1956. The increases in 1958 and 1959 are in proportion to the increased number of admissions and births as evidenced by the fact that the incidence of infection for 1957, 1958 and 1959 was 0.9%, 1.1%, and 1.0%, respectively. The incidence of infection in 1956 was 1.6%. These results might indicate that our control measures were partially effective, but which if any is unknown.

INFECTIONS INDUCED BY TYPE 80/81. The observation of a decreased frequency of the 80/81 strain in all cate-

gories of hospital acquired infections in 1959 is not entirely understood. In spite of this decrease, the 80/81 type still remained the predominant single type of staphylococcus causing infection in the hospital. Because this decrease was offset by a relative increase in other phage types, it would be tempting to say that 80/81 was being replaced by some other type. Apparently this happened in Texas where 44A replaced 80/81 (Windom *et al.*[11]). But a review of all other phage types causing our infections in 1959 did not reveal any one to be common enough to validate this assumption. It will be interesting to note if this apparent trend toward disappearance of type 80/81 materializes as fact in the ensuing years.

Some of the other phage types in 1959 might actually be 80/81 which in 4 years has for several reasons taken on a different susceptibility to the phages. Phage typing relies upon an interaction of 2 biologic entities, the coccus and the phage, each of which is subject to change by mutation. Many, if not all, of the staphylococci isolated in nature are lysogenic, that is, carrying a phage, and lysogeny is known to prevent penetration of the phages used in typing. The importance of this fact is borne out by Rountree's findings that 52/52A/80/81 staphylococci of recent isolation or from the famous Bundaberg disaster may under proper conditions type as 80/81 or as one of several other types (Rountree[7]). This means that phage typing lacks the specificity that would be desired for a system of identification. However, it is the best method yet available for staphylococci and is certainly useful when due regard is paid to the difficulty of interpretation of results.

ANTIBIOGRAM. The changes in the the antibiogram of the 80/81 type over a 3-year period are those which might have been anticipated. It has frequently been observed that staphylococcal resistance to a given antibiotic increases with the use of that antibiotic. Because the 1956 antibiogram showed good susceptibility to chloramphenicol and novobiocin, both antibiotics were used quite extensively with the result that in 1959 substantial resistance to each was detected (Fig. 9). A slight change toward susceptibility of 80/81 to erythromycin was correlated with little use of that drug. Figure 9 shows a return towards susceptibility of other phage types to penicillin and tetracycline, but this cannot be so interpreted because these antibiotics probably have not been used less frequently. Rather this observation perhaps indicates infection with strains which were more recently introduced into the hospital.

The disparity of resistance to penicillin 152 at 18-hours and 48-hours incubation indicates that at 18 hours this agent is holding the staphylococcus in bacteriostasis. This may happen either because penicillin 152 has the ability to withstand the action of penicillinase longer than does penicillin G or because the "synthetic" penicillin retards penicillinase production. What significance this observation may have in clinical use remains to be determined.

TRANSMISSION OF THE ORGANISM. Four years' experience permits certain inferences to be drawn both on a negative basis where lack of evidence has failed to substantiate a suspected mode of transmission and on a positive basis. As already indicated, the failure to detect the 80/81 staphylococcus with any regularity or in appreciable numbers in the inanimate environment including the air relegates this possible source still to the realm of speculation. The apparent lack of 80/81 from the environment of this institution cannot be ascribed to any new or radical

change in housekeeping technique because as indicated above none was established.

No evidence has been obtained to indict airborne contamination of open wounds at surgery. The report from Shouldice Surgery (Browne *et al.*[2]) which tends to incriminate this route during surgery was more likely an example of implantation of droplets or droplet nuclei directly from the nose of a "dangerous" nasal carrier. It should therefore be an example of transmission by close personal contact.

At the onset of our study it was noted that a very small number of our personnel were carriers of the 80/81 type. This observation of a low nasal carrier rate has subsequently been made by others (Mitchell *et al.*[5]). We tended, therefore, not to subscribe to the role of significance which had previously been assigned to nasal carriers. The 4 years' experience has produced no evidence to incriminate nasal carriers as important vectors of the organism. This has remained true even in the most recent study of nursery personnel in which 6 carriers of 80/81 were found but no infection of babies occurred. As previously reported (Schreck *et al.*[8]), the patient with a staphylococcus in his nose prior to surgery rarely develops an infection postoperatively with the organism he carried. Thus in the opinion of the author, negative findings point to the remoteness of importance of the inanimate environment and healthy nasal carriers as a source of the organism for the patient.

On the other hand, great significance has been attached to the transmission by close personal contact with infected personnel and patients. It has been shown that a surgeon with an active infection may have 18% of his operations develop sepsis with the same phage type of staphylococcus that caused his lesion (Mitchell *et al.*[5]). Nothing has occurred during the 4 years to detract from personal contact as being the most important mode of spread. Figure 6 shows fewer of our personnel acquired their first infection in 1959. Yet in that year, we had the second highest total number of patient infections incident to hospitalization. This interrupted a trend seen in the first 3 years of the study, that is, patient infections paralleled personnel infections. This discrepancy in 1959 might mean that more patients acquired their infections from patients admitted with infection than they did from personnel. In support of this idea is the fact that more patients were admitted with infection in 1959 than ever before (Fig. 7). Furthermore it is noted that 53% of the patients admitted with infection in 1959 had other phage types as the etiologic agent; this could account for the fact that other phage types increased in all categories of hospital infections in that year.

Thus the point just developed is that personal contact is the most important means of transmission of the organism and that in the fourth year of this study perhaps more contact occurred with infected patients than with infected personnel. If this idea is correct, it makes isolation mandatory before the problem of staphylococcal infection will be brought under control.

DIFFERENCE BETWEEN 80/81 AND OTHER TYPES. Unpublished experimental results failed to produce any conclusive evidence of difference in virulence of various types of staphylococci for laboratory animals. The author has not assumed the 80/81 type to be more virulent for the human because no test for virulence is available. Clinically the lesion produced in the skin of humans by type 80/81 does appear to be different from the abscess produced by other types. This difference is manifest

in a wider area of inflammation and pigmentation surrounding the lesion which in turn is less productive of pus. However, the type 80/81 has no predilection to produce a special type of infection or to produce bacteremia any more frequently than other types.

The 80/81 type does, however, have an apparently greater tendency to persist with the patient either in the same lesion or in recurrent lesions. As noted previously, 10 of the 11 patients in this series who were troubled the longest with recurrent infections were hosts to the 80/81 type. A phenomenon related to persistence is the transmission to and infection of other members of the patient's family. We have many instances in which patients have gone home and transmitted the organism to others in the family. Similar occurrences have also been noted in the families of several staff members, most notably pathologists. Almost without exception, the organism in these cases is the type 80/81. Thus it appears that this strain is more easily transmitted in numbers sufficient to produce infection and once acquired by a patient will persist longer than other types of staphylococci. However, it should be noted that the mere presence of type 80/81 is not tantamount to infection (Fig. 11). Apparently this type may persist in the noses or on the skin of infants and adults and not produce infection.

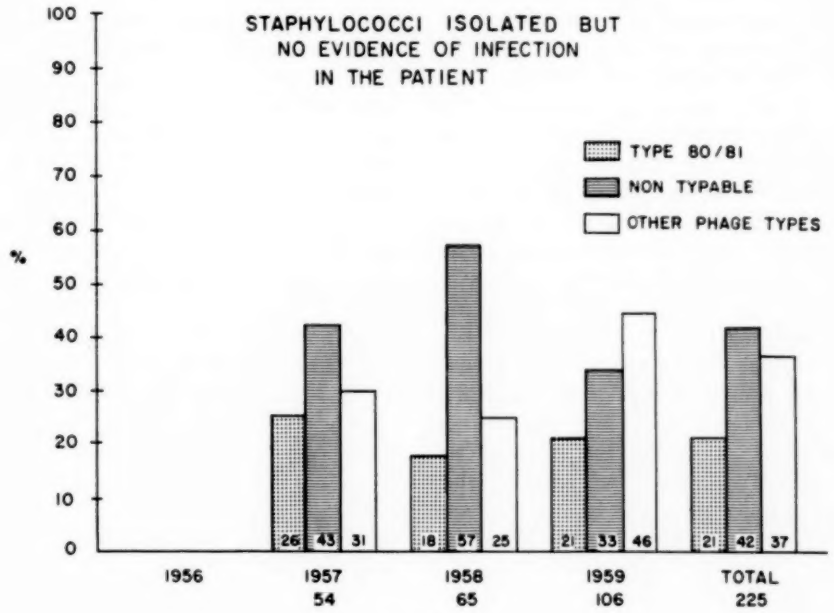


Fig. 11

In 270 cases where sufficient evidence was available to make the decision, it was found that very infrequently was the original infecting staphylococcus replaced by another type of staphylococcus. In the 3 instances where replacement did occur, the change was to the 80/81 type. This finding of apparent "exclusion"

is somewhat similar to the observations made with the serotypes of *E. coli* in the gut (Sears *et al.*[10]).

THE HOST. It has usually been assumed that some abnormality exists in the host to permit his infection. As mentioned above, the surprising observation was made that diabetic patients had the same incidence of infection in the hospital as did the non-diabetics. So the diabetic patient was at no greater risk in spite of the fact that 12% of the patients admitted to the hospital with infection had diabetes.

It is also commonly assumed that the older age groups are more prone to infection by the staphylococcus. But Fig. 10 shows the peak of infections to have occurred in the decade 51 to 60. To have significance, this graph would have to be compared with the age distribution of all patients admitted for the same period. Unfortunately such data are not maintained and are therefore not available. But I should imagine that Fig. 10 is very close to representing the age distribution of all admitted patients. If that be true, there then would not exist any age predilection to infection. This idea would certainly be borne out by the large group of our young, healthy student nurses who have become infected.

Evidence pointing to any peculiarity of the host leading to infection has thus not been obtained in the areas sought. These 4 years have indicated to the author that regardless of one's age, sex, hormonal balance, state of nutrition, or the season, the presence of the 80/81 staphylococcus on the skin in an area which will be slightly traumatized by a rubbing shirt cuff, underwear band, girdle, bed, auto seat, and so forth, will lead to abscess formation. The robust person "immune" to staphylococcal infections is probably simply "immune" because he does not have the organism present on the skin or on the right area of his skin to develop an infection.

Summary. The experience of a 4-year prospective study of hospital acquired staphylococcal infections has been examined for information relative to the epidemiology of such infections. It has been noted that there was a real decline in total number of infections in 1957, the second year of the study. Since then, there has been a yearly progressive increase in total infections but only in proportion to the increase in total admissions. The incidence of hospital acquired infections was 1.6% in 1956 and between 0.9% and 1.1% for 1957, 1958 and 1959.

In the fourth year, there was a relative decrease in infections caused by the 80/81 type and this decrease was offset by an increase in other phage type infections. It is noted that this shift could have been brought about by a change in the staphylococcus causing it to type differently by the phage method which is not an ideal means of identification but the best available. However, this shift was more likely manifest because of greater patient to patient transmission; several points in support of this idea are discussed.

The change in antibiogram is discussed. Greater resistance to chloramphenicol and novobiocin was detected in the fourth year of the study.

No particular phage type of staphylococcus has the propensity to cause a given type of infection. About 4% of all hospital acquired infections developed bacteremia regardless of the phage type or the category of infection. Diabetic patients admitted to the hospital without infection were at no greater risk of developing infection in the hospital than were non-diabetic patients. Excluding infants, age prob-

ably had no influence on the acquisition of infection. The peak infections occurred in the age group 51 to 60.

The importance of the environment as opposed to the human source of the organism is discussed.

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SUMMARIO IN INTERLINGUA

Observationes Super le Epidemiologia de Infectiones Staphylococcal

Le experientias de un quadrienne studio "prospective" (non: "retrospective") de infectiones staphylococcal acquirite al hospital esseva scrutinate pro informationes relative al epidemiologia de tal infectiones. Il esseva notate que un ver declino in le numero total de infectiones occurreva in 1957, le secunde anno del studio. Ab ille tempore le numero total de infectiones ha montate progressivemente ab un anno al altere, sed non foras de proportion al augmento in admissiones total. Le incidentia de infectiones acquirite in le hospital esseva 1,6 pro cento in 1956 e inter 0,9 e 1,1 pro cento in le annos 1957, 1958, e 1959.

In le quarte anno le proportion del infectiones causate per le typo 80/81 de streptococco decresceva, sed iste reduction esseva contrabalanciate per un augmento in infectiones per streptococcos de altere phagotypos. Il es notate que iste redistribution pote esser le resultato de un alteration intra le streptococco e un consequente alteration in su reactiones al lysotypia, que non es un methodo ideal sed le melior nunc disponibile. Nonobstante, il es plus probabile que le alterate distribution reflecte un plus grande transmission ab un patiente al altere; varie punctos in supporto de iste idea es discutite.

Le alteration del antibiogramma es discutite. Un plus grande resistentia a chloramphenicol e a novobiocina esseva detegite in le quarte anno del studio.

Nulle phagotypo particular ha le propensitate de causar un typo particular de infection. Approximativemente 4 pro cento de omne infectiones acquirite in le hospital resultava in bacteremia sin reguardo al phagotypo o al categoria de infection. Patientes diabetic admittite al hospital sin infection non curreva un plus grande risco de disveloppar un infection in le hospital que le patientes non-diabetic. Con le exception del infantes le etate probabilemente habeva nulle influentia super le acquisition de infection. Le incidentia maximal del infectiones occurreva inter le etates de 51 e 60 annos.

Es discutite le importantia del ambiente per contrasto con illo del donator human del organismos.

THE RELATION BETWEEN DIABETES MELLITUS AND INFECTIONS OF THE URINARY TRACT

A CLINICAL, QUALITATIVE AND QUANTITATIVE BACTERIOLOGICAL STUDY BASED UPON 300 DIABETICS AND 200 CONTROLS

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Infections of the urinary tract have long been known to be a frequent and serious complication in diabetes. Purulent urinary tract infection was present in 18% of the necropsy material of Sharkey and Root[11] reported in 1935. According to the records of Joslin[6] it occurs in about 20% of the cases, whereas Young and Clancy[12] found infections of the urinary tract in 42% of their diabetic necropsies.

Kass[8] detected bacteriuria, 100,000 or more bacteria per milliliter of urine, in 18% of diabetic outpatient females, and 5% in males, whereas only 6% of women and 4% of men had the same degree of bacteriuria in the medical outpatient clinic of the Boston City Hospital. Edmondson, Martin and Evans[3] reported urinary tract infections causing various symptoms in 107 of their 859 diabetics. Keefer[9] found pyelonephritis in diabetic patients about four times as often as in nondiabetic patients. He believes that diabetes is a predisposing factor comparable to renal calculi, renal tumors and obstructions of the lower urinary tract. According to Heténvi[4], despite the advent of insulin, pyelonephritis occurs twice as frequently in diabetic persons as in the nondiabetic population. Joslin[6] suggests that since the introduction of insulin, pyelonephritis has become rare, but he still maintains that diabetes predisposes to infections of the urinary tract, and so he as well as others warn against the hazards of catheterization of diabetic patients without premedication with potent antibacterial drugs. Recently Lipscomb, Dobson and Greene[7] have pointed out the increased incidence of genitourinary infection in diabetic compared to nondiabetic persons. Huvos and Rocha[5] studied the bacterial counts in the "clean-voided" urines of 50 diabetic patients and 50 controls. They found a high percentage of pathological bacteriuria in both groups (34% and 26%).

In our diabetic outpatient clinic established 11 years ago we were astonished to observe that the patients rarely complain of symptoms pointing to infections of the urinary tract. We decided, therefore, to study the frequency and seriousness of genitourinary infections in our diabetic patients using qualitative and quantitative bacteriological methods.

Material and Methods. The present paper reports the observations made on 300 diabetic patients, 208 females and 92 males respectively. Two hundred nondiabetic patients, 116 females and 84 males in whose history no renal disease and no factor predisposing to urinary tract infection could be detected, served as controls. Neither the controls nor the diabetic patients had recently received antibacterial treatment.

From the majority of the diabetic patients the urine was obtained in the outpatient clinic. The controls were selected from the wards. The women were subjected to careful sterile catheterization, the men produced "mid stream" specimens. The urine specimens were analyzed for protein and sediments, qualitative bacterial cultures were carried out on agar plates within 2 hours, and living bacterial counts made by dilution method in bouillon containing lactose and Andrade indicator. (Method modified by Balázs and Cserháti[1].)

The patients were divided into groups according to their sex, the type of the treatment, the duration of the diabetes and the severity of the glycosuria. The severity of the glycosuria was determined by repeated examinations and the diabetic patients were divided into 3 categories. We classed as "well controlled" those patients who cooperated suitably and never excreted more than 20 gm. of sugar in 24 hours. The "adequately controlled" patients sometimes excreted more than 20 gm., but their excretion never exceeded 40 gm. We classed our "brittle" diabetic patients only "adequately controlled" because their glycosuria varied between wider limits. "Bad control" means lack of cooperation and glycosuria frequently exceeding 40 gm. in 24 hours.

The patients maintained on diet alone, those treated with carbutamide, and those who received insulin were studied separately. Carbutamide (Bucarban, Chinoin) was always administered intermittently (7 to 10 days in each month).

Results and Discussion. The purpose of our investigations was to answer two main questions: 1) How frequently clinically-manifested urinary tract infection occurs among our diabetic patients, and 2) the susceptibility to this complication of diabetic patients *not* having active urinary tract infection.

1) Massive pyuria with proteinuria and significant bacteriuria (greater than 10,000 bacteria per ml. of urine) was found in 9 patients (3%). In 9 other patients significant bacteriuria without proteinuria, pyuria, fever and subjective complaints was observed. If we assume that these cases may be due to a monosymptomatic urinary infection, in our cases the percentage rises to 6.

TABLE 1.—AVERAGE BACTERIAL COUNT IN THE URINE OF DIABETIC PATIENTS AND CONTROLS

	Diabetic patients		*Controls*	
	♀	♂	♀	♂
Number of patients	202	98	116	84
Bacterial count log ml.	1.77	2.44	0.86	1.93

2) In the urine of the 300 diabetic patients the average bacterial count was log 1.98 per ml. and in the control specimens log 1.31 per ml. The difference does not change essentially if the bacterial count of the patients suffering from active urinary tract infection is disregarded. According to the published data (Merritt and Sanford[10]) and to our previous experiments[1,2] patients with more than 10,000 to 100,000 bacteria, log 4 to 5 per ml. may be regarded as suffering from true infection, so the difference between the bacterial counts of the two groups seems insignificant. The cause of this slight difference should however pro-

vide the answer to the second question.

The average bacterial count in the males was higher in both the diabetic and control groups than in females (Table 1). This can be explained by the fact that in the case of males "mid stream" voided urines were investigated, and so the bacterial flora of the urethra may have contaminated the specimens.

Figure 1 shows that although the average bacterial count in diabetic males is higher than in the controls, the two curves run pretty closely, and comparatively few cases can be found exceeding log 4 per ml.

Figure 2 shows that sterile specimens were found much more rarely among diabetic females than in the control group, and that the curve

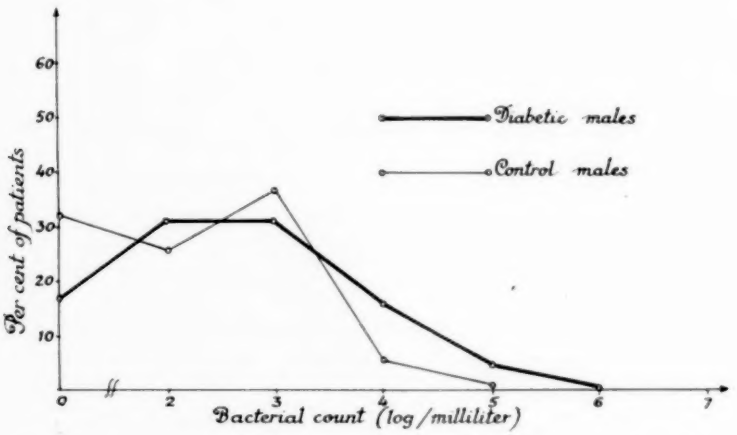

Fig. 1.—Bacterial count in the urine of diabetic and control males.

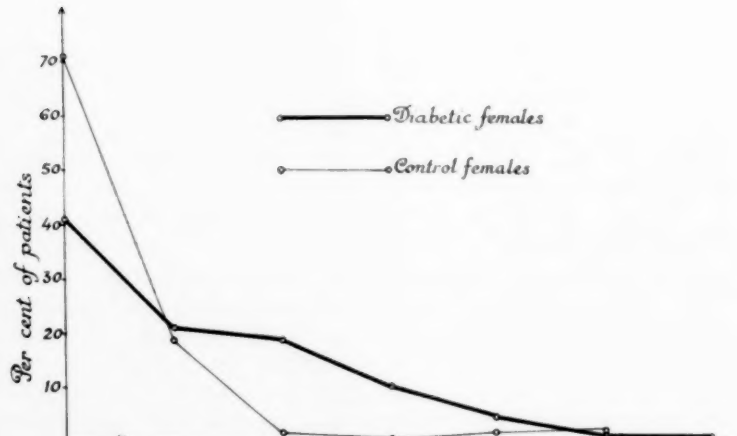

Fig. 2.—Bacterial count in the urine of diabetic and control females.

characterizing the diabetic females runs higher from log 2 per ml. on, whereas living bacterial counts exceeding log 3 per ml. could hardly be observed among the controls.

In order further to analyze this difference, Fig. 3 shows the diabetic females divided into groups according to the severity of their glycosuria. The peak of the curve of the "well controlled" group appears at zero, that is: sterility, and is quite similar to that of the controls. The "badly controlled" group behaves quite differently. Its curve starts low at zero and reaches its peak towards the pathological bacterial counts. The curve of the "adequately controlled" group runs between the two.

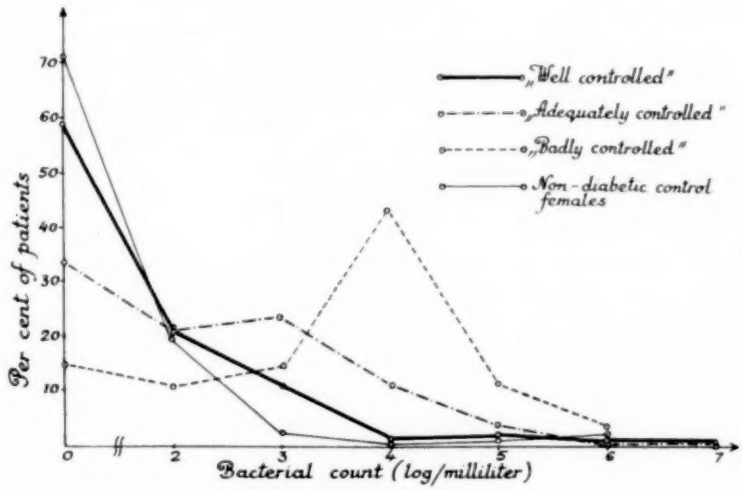

Fig. 3.—Relation between the urine bacterial count and degree of glycosuria in diabetic females.

In the course of our studies we have made a few additional observations:

a) The composition of the bacterial flora shows a significant difference between the group with the high bacterial count and that with the low one. In cases of marked bacteriuria in this and other (Young and Clancy[12]) material, *E. coli* was the most common organism isolated, whereas the bacterial counts under 10,000 per ml. were composed of mixed flora (mostly Gram-positive cocci: staphylo-, enterococci and tetragenus; and sarcina and very rarely *Monilia albicans*). *E. coli* could be found only in a low percentage in this group.

b) The type of treatment did not influence the bacterial count (Table 2). There is no striking difference between the groups treated with diet alone and those in which carbutamide or insulin was administered.

c) There is no essential relation between the duration of the diabetes and the living bacterial count (Table 3).

d) Of 22 patients suffering from Kimmelstiel-Wilson's syndrome the urine of 13 proved sterile. The average bacterial count in this group was log 1.45 per ml., a figure approaching more that of the control group than that of the diabetic patients. This seems to indicate that diabetes complicated by Kimmelstiel-Wilson's syn-

drome does not predispose to infections of the urinary tract.

The results of our investigations suggest the following conclusions:

Clinically active urinary infection is *not* more frequent among diabetic persons than in the average population. The behavior of patients not suffering from active infection is not uniform: we could not prove any predisposition to infection in the "well controlled" group, whereas "badly controlled" diabetic patients, at least the females, seem more susceptible to bacteria. Consequently we suggest that the old statement, that urinary tract infection is more frequent in diabetic persons needs revision. The diabetic state itself does not involve predisposition to urinary infection; the important factor is good control of the disease.

We believe that the regular control of diabetes performed at the outpatient clinic is a potent means for the prevention of infection. The education and training of the patients can be carried out there routinely. Even the diabetic patients with a high degree of glycosuria are not neglected owing to the constant medical care. Regarding the prevention of infection, these patients are nearly in the same position as the patient with aglycosuria.

Summary. Urine specimens of 300 diabetic and 200 control patients were analyzed for proteinuria, pyuria and bacterial count.

1) Significant bacteriuria was found in 6% of the diabetic patients. This does not differ essentially from the results obtained by other authors in the normal population.

2) The living bacterial count in the urine of diabetic patients was higher than that observed in the controls, but did not reach pathologic values.

3) The curve of the bacterial counts of "well controlled" diabetic patients ran close to that of the controls, whereas that of the "badly controlled" patients approached pathological values.

4) In cases of active infection, *E. coli* was the most frequently isolated

TABLE 2.—RELATION BETWEEN TYPE OF TREATMENT AND URINE BACTERIAL COUNT (log per ml.).

	Diet only	*Insulin*	*Carbutamide*
Males	2.50	2.39	2.54
Females	1.80	1.88	1.52

TABLE 3.—RELATION BETWEEN THE DURATION OF DIABETES AND THE URINE BACTERIAL COUNT (log per ml.).

Duration of diabetes in years	*Average bacterial count of females*	*Average bacterial count of males*
<1	2.08	2.78
1–5	1.72	2.45
6–10	1.57	2.17
11–15	2.14	2.16
>16	1.78	2.70

microorganism. The low bacterial counts of the controls and noninfected diabetics were composed mostly of Gram-positive cocci.

5) Very similar bacterial counts were observed in specimens of patients treated with diet alone or with carbutamide (intermittently) or insulin.

6) Among 22 patients suffering from Kimmelstiel-Wilson's syndrome the urine of 13 was sterile, and even the bacterial counts of the contaminated ones were nearer to those of the controls than to those of the other diabetic patients.

7) On the basis of the above data it is suggested that the old concept that urinary tract infection is more frequent in diabetic patients should be revised. The susceptibility of the urinary tract of diabetic patients, especially of females, to bacteria seems nevertheless greater. The regular control of these patients prevents these cases from developing clinically active infection.

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(Interlingua on page 170)

SUMMARIO IN INTERLINGUA

(See page 192 for original article)

Tractamento de Pneumonia Pneumococcal con un Nove Penicillina: Observationes Clinic in 25 Patientes

(1) Vinti-cinque patientes con pneumonia pneumococcal esseva tractate con le nove partialmente synthetic penicillina alpha-phenoxyethylic a kalium.

(2) Le resultatos esseva eminentemente satisfacente in omne casos. Il habeva nulle mortes, nulle complicationes purulente, nulle adverse reactiones ab le droga mesme.

(3) Le dosage in le ultime 11 subjectos del gruppo esseva 250 mg per via oral, tres vices per die, con omne doses administrate inter repastos. Le resultatos in iste patientes esseva tanto bon como in le prime 14 casos, qui recipeva plus grande doses.

(4) Si prescribite correctemente, penicillina alpha-phenoxyethylic a kalium es un bon preparato que es tanto efficace como non importa qual altere producto in le tractamento de pneumonia pneumococcal.

TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH A NEW PENICILLIN: CLINICAL OBSERVATIONS IN 25 PATIENTS*

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Penicillin is the drug of choice in the treatment of patients with pneumococcal pneumonia. It should not be replaced by other antipneumoccal agents, for example, erythromycin, tetracycline, chloramphenicol or a sulfonamide, except in the unusual and uncommon instance of intolerance.

Penicillin can be given in a number of ways, by a variety of routes, in widely disparate dosage schedules and for varying lengths of time for treatment of this acute infection and virtually all reported regimens have proven good; there is no best one. Similarly there are available many kinds of penicillins and most of them can be used successfully for therapy of pneumococcal pneumonia. At the recent Antibiotic Symposium a new, partially synthesized, penicillin was described, potassium alpha phenoxyethyl penicillin (Pindell *et al.*[2]). We have used this material exclusively for the management of 25 consecutive cases of bacteriologically confirmed pneumococcal pneumonia and have found it to be an effective penicillin. This report summarizes these experiences.

Materials and Methods. THE DRUG. Potassium alpha-phenoxyethyl penicillin is prepared by the usual fermentation process which yields the skeleton 6-amino penicillanic acid, to which is synthetically added the chemical side chain. It is marketed under the proprietary name of Syncillin, Bristol. We have studied it in the laboratory as number BLP152 and it is referred to by that number in this report. When administered to humans by the oral route, absorption into the blood stream is prompt and excretion via the kidneys is, as with other penicillins, rapid†. Following a 268-mg. dose, which is the molecular equivalent of 250 mg. phenoxymethyl penicillin (V) and of 400,000 units (240 mg.) penicillin G, serum levels above 2.5 μg. per ml. are attained within an hour. Concentrations above .05 μg. are maintained in serum for from 4 to 5 hours. Within 24 hours approximately 35% of the administered dose can be recovered in the urine. Distribution of the drug into pleural fluid is essentially the same as that observed in the blood. In these properties BLP152 is very similar to penicillin V, but significantly different from penicillin G. Its absorption from the intestinal tract, although no more prompt, is more complete than G and more of a dose is excreted. Thus more is available in the body for its antibacterial activity than is true with an identical dose of penicillin G.

Dosage of BLP152 for treatment of patients with pneumococcal pneumonia was designed from these observations of its pharmacologic properties. Initially, 500 mg., 4 times daily was prescribed (Table 1). This amount gave blood levels significantly in excess of 0.05 μg. for about 20 hours each day. These levels were not considered to be necessary, consequently later patients received less, that is, 250 mg., 3 times daily. This amount provided concentrations in serum above 0.05 mg. per ml. for at least 4

*Work supported by a grant from Bristol Laboratories, Inc., Syracuse, New York, and the drug used was supplied by them.

†All pharmacologic work was done in our own laboratories.

hours after each dose. Pneumococci are equally susceptible to BLP152 as with other penicillins; in fact they are completely inhibited by appreciably less than .05 μg. per ml. As the recovery phase of their growth, following cessation of exposure to penicillin, does not recommence for at least 6 hours,

TABLE 1.—DRUG REGIMEN IN 25 PATIENTS WITH PNEUMOCOCCAL PNEUMONIA TREATED WITH ALPHA PHENOXYETHYL PENICILLIN

	500 mg. 3 or 4 Times Daily	*500 mg. 3 Times Daily for 1 to 3 Days, then 250 mg. 3 Times Daily*	*250 mg. 3 Times Daily*
No. of pts.	3	11	11

the regimen of 250 mg., 3 times daily, was considered adequate to provide effective antipneumococcal activity for the patient (Bunn *et al.*[1]).

Therapy was extended for from 7 to 22 days and the duration was dependent mainly upon an infected individual's clinical response.

THE PATIENTS. Twenty-five adult patients all hospitalized with pneumococcal pneumonia were treated with a phenoxyethyl penicillin (Table 2). Ages ranged from 18 to 86, there were 5 females, 20 males; 4 were colored. Bacteremic state was present at the time treatment was started in 5 (25%). No purulent complications were evident at time of hospital admission, none appeared during treatment. All patients were acutely ill, many (13) morbidly so. No one, however, was in shock. Associated diseases were varied and severe in 10, cirrhosis, heart failure, malignancy and acute alcoholism (Table 3). In 8 others there were accompanying health problems of a less important nature, for example, emphysema, asthma, chronic bronchitis, arthritis, compensated heart disease and, perhaps, Asian influenza.

Pneumococci were identified in the sputum of each of the patients upon admission to the hospital and cultured proof was obtained in 22. Sputa from 3 patients were lost somewhere between the patient and the laboratory, but in each the stained smear of the initial sputum revealed classical, encapsulated Gram-positive diplococci. Clinical and roentgenographic disease in these 3, like all of the others, was compatible with the diagnosis of pneumococcal pneumonia.

TABLE 2.—25 PATIENTS WITH PNEUMOCOCCAL PNEUMONIA TREATED WITH ALPHA PHENOXYETHYL PENICILLIN

On Hospital Admission	*17-30*	*31-50*	*51-70*	*70*	*Total*
Number of patients	5	4	11	5	25
Number with:					
Two or more lobes involved	1		4		5
Positive blood cultures	—	1	1	3	5
Temperature over 103° F.	5(2)*	2	7(1)	2(1)	16
Leukocytosis over 12,000	5	2	8	3	18
WBC less than 10 000	—	2	2	2	6
Duration disease before Rx					
1-3 days	3	3	8	3	17
4-7 days	2	1	3	2	8

*( ) number with temperature over 104° F.

Other clinical features of the 25 patients are noted in Tables 2, 3, and 4.

Results. All patients recovered, there were no deaths and no purulent complications. There were no untoward side effects from the drug itself; each patient completed his prescribed course of treatment.

Fever subsided in the majority (13) within 40 hours by crisis. Slow defervescence was observed in the others

(Table 4). Normal temperatures were experienced by all within one week and no clinical relapses occurred. As has been pointed out by others (Bunn *et al.*[1]), not infrequently a rapid crisis was followed 12 to 24 hours later by a rise in temperature to 101 to 101.5°, that time (15). Blood cultures, originally positive in 5, were all negative within 24 hours.

Resolution time varied considerably. In the young and in those with no associated severe heart or chronic lung disease (15), clearing of the pneu-

TABLE 3.—ASSOCIATED DISEASES IN 25 PATIENTS WITH PNEUMOCOCCAL PNEUMONIA TREATED WITH ALPHA PHENOXYETHYL PENICILLIN

Disease	*Number of Patients*
Heart disease	4 (1 in failure)
Cirrhosis or acute alcoholism, or both	3 (1 with liver failure & ascites)
Chronic pulmonary disease (noninfectious)	3
Carcinomatosis	2
Leukemia or severe anemia, or both	2
Crippling arthritis	1
Questionable Asian influenza	3
No disease	7

TABLE 4.—RESPONSES IN 25 PATIENTS TREATED WITH ALPHA PHENOXYETHYL PENICILLIN FOR PNEUMOCOCCAL PNEUMONIA

*Acuteness of Illness at Start of Therapy**	*Total No. of Patients*	*Crisis of Fever Within 40 hrs.*	*Slow Resolution (Roentgen-ray)*	*Duration Hospital Stay (days)*			*Response**	
				<7	*8-15*	*16-27*	*Excellent*	*Satisfactory*
Severe	13	9	5	4	7	2	10	3
Acute	12	4	5	2	8	2	5	7
Total	25	13	10†	6	15	4	15	10

*Arbitrary and personal clinical impression.

†Seven of these 10 were the only ones to receive treatment longer than 7 days. Longest treatment period was 22 days.

which promptly subsided. In one patient an unexplained rise to 101.5° occurred in the 5th day of treatment. This settled down spontaneously after 24 hours without change in treatment nor with the appearance of any complication.

Pneumococci disappeared from the sputum by the second day in all patients whose sputa were restudied at

monia by Roentgen-ray examination and by physical signs was appreciable by the 5th day, and complete resolution occurred by the 14th day. In the remaining, resolution was slower and in 5 clearing was continuing at the time of discharge from the hospital, 18 to 27 days after admission. By the gross techniques used for its measurement, inadequate resolution with organiza-

tion and fibrosis was not observed; detailed pulmonary function studies were not carried out.

Sputa of 5 patients revealed organisms other than pneumococci after 4 days of treatment with BLP152. *Hemophilus influenzae,* Klebsiella, Neisseria and Staphylococci were isolated but in no patient was their presence associated with a change in the clinical picture, nor indeed was the pattern of resolution altered in these patients. Chloramphenicol was added to the regimen in 2 of these on the 5th and 6th days. Its addition did not alter the otherwise favorable course of the infection in either.

Duration of hospital stay varied from 5 to 27 days. The time of discharge was directly related to speed of crisis, speed and completeness of resolution and the success of remedies for associated disease states. In the 4 whose hospital stay extended for more than 20 days, one had carcinoma of the liver, another had cirrhosis with ascites, the third had an unexplained hemolytic anemia, present before the administration of penicillin, which required an extensive hematologic study. The remaining patient had chronic lung disease and his pneumonia resolved slowly. The infectious part of the acute pneumonia in these 4 patients was clinically controlled within a week.

Although 3 regimens were used, 500 mg., 4 times daily, a large then smaller amount after the second or third day, and 250 mg., 3 times daily, there appeared to be no essential difference in the results. Gastrointestinal function was adequate throughout the illness in every patient.

Discussion. In Table 3 there is noted that 3 of the patients may have had Asian influenza prior to the development of pneumococcal pneumonia. Two of the patients were under 30 years, the other 45. Asian influenza had been prevalent in Syracuse during the period of this study (October, 1959, to January, 1960). Although no serological tests nor attempts at isolation of the virus was made in these 3, each had an acute respiratory ailment prior to the onset of the pneumonia. The preceding infection was classical of influenza with aching, cephalalgia, hacking nonproductive cough, slight fever and severe malaise. The presumption that the 2 infections (pneumococcal pneumonia and influenza) were closely associated in these 3 individuals lacks proof and remains then a presumption.

The evaluation of a chemotherapeutic agent in pneumococcal pneumonia is not a troublesome problem. The disease is reasonably predictable and a well defined baseline of what to expect with a good therapy has been reported innumerable times (Bunn *et al.*[1], Tompsett *et al.*[3]). Speed of crisis, promptness of resolution of parenchymal lesions, duration of clinical illness, rapidity of disappearance of organisms from the sputum or blood, or both, mortality and incidence of purulent complications are all clear indices for evaluation of any therapeutic program. Similarly, when comparisons of efficacy are made among the many available penicillin products, no one of them has achieved such a superior position in management of patients with pneumonia that other preparations should be discarded. One would be hard pressed, if not foolish, to label any single penicillin product best as far as antipneumococcal activity is concerned. Phenoxyethyl penicillin (Syncillin) has proved itself to be as efficacious and its use in the treatment of pneumonia can be recommended, without hesitation or reservation. Furthermore it can be used, because of its pharmacologic properties in reasonably small daily doses, for ex-

ample, 250 mg., 3 times daily, if each dose is given at a time when the stomach is free from food. As is true with any orally given therapy the gastrointestinal tract, as a whole, must of course be functioning normally.

Hypersensitivity reactions to penicillin G represent the major, if not sole, hazard to its use in the human. Although we have seen no allergic phenomena develop in these 25 patients, it is logical to presume that such will eventually occur. There seems to be no chemical or logical reason to believe that this new product is hypoallergenic. On the other hand, we have observed (but not in this series of cases) that alpha phenoxyethyl penicillin can be given to patients having had or having untoward skin reactions to penicillin G, without either exacerbation or continuation of that reaction. In this sense, one can presume that, with first exposure to this new agent, there is no cross reaction with the older product. It would be delightful if that comforting state of affairs would continue to be true. However, the few observations which we have made so far should not lead to a sweeping conclusion; we consider that the lack of allergy in our patients has been strictly fortuitous. There were no deaths in this series; this is an indication that none of the individuals were as critically ill as is true with some patients in most other published series (there is an accepted 5 to 7% mortality rate for pneumococcal pneumonia). We do not imply that the 100% survival suggests that the new penicillin is better than others. Similarly, no patient had an ileus which would have precluded the use of an oral preparation for specific treatment.

Summary. 1) Twenty-five patients with pneumococcal pneumonia have been treated with the new partially synthesized potassium alpha phenoxyethyl penicillin. 2) Results were eminently satisfactory in all. There were no deaths, no purulent complications, no untoward reactions from the drug itself. 3) Dosage schedule was, in the last 11 of the group, 250 mg. orally, 3 times daily, with each dose given between meals. Results in these were as good as the first 14, who were treated with larger amounts. 4) If prescribed properly, potassium alpha phenoxyethyl penicillin is a fine preparation, as effective as any product for the treatment of pneumococcal pneumonia.

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(Interlingua on page 191)

BEHAVIORAL TOXICITY OF EMYLCAMATE (STRIATRAN)

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Emylcamate* is a psychoactive drug with internuncial blocking action, and a spectrum of anticonvulsant activity resembling that of meprobamate. Preliminary animal and clinical screenings have indicated its probable usefulness in the treatment of tension, anxiety and other neurotic symptoms. Its action would appear to be most similar to that of those tranquilizers commonly used in outpatient treatment.

The present study was designed to test the acute behavioral effects of several dose levels of emylcamate on normal subjects. We examined particularly behavioral toxic effects that might contraindicate administration of the drug to an outpatient who must continue to perform such day-to-day duties as driving a car or working at a machine. The driving, vision, and steadiness battery used in a number of previous studies on behavioral toxic drug effects was employed for this purpose (Marquis, Kelly, Miller, Gerard and Rapoport, 1957[4]; Kelly, Miller, Marquis, Gerard and Uhr, 1958[1]; Miller and Uhr, 1959[5]; Uhr, Pollard and Miller, 1959[6]). In a study to be reported later, positive drug effects of emylcamate were explored by measuring performance on a wide range of simple cognitive, psychomotor and attention tests administered to subjects while they were under laboratory-induced stress.

Method. All subjects were tested under all drug treatments (thus serving as their own controls), according to a counterbalanced design. Capsules of identical appearance and taste were administered in a "double-blind" manner. All subjects were given a session of practice on tests in which learning might occur. The training session was followed by four test sessions, with from one to 3 days between sessions. All subjects were scheduled so that their test sessions were always held at the same time of day.

Forty-nine subjects completed all sessions of the experimental run; 6 additional subjects completed all sessions in a pre-test run. Three subjects dropped out of the study after their first test sessions. They were replaced, according to counterbalancing procedures, by additional subjects in subsequent groups. But the subject who dropped out of the final group could not be replaced by any of the extra subjects run without leading to a slight discrepancy from the counterbalancing schedule. So two extra replacements were used, bringing the group up from the counterbalanced 48 to a total of 49. Because of the large number of subjects tested in the study, this slight discrepancy from the original had no discernible effect.

All subjects were prisoners at the State Prison of Southern Michigan. They were prescreened on the basis of prison records for average or higher intelligence (IQ of 105 or above), and for having no recognized medical disability. They were then asked to

*In the United States, emylcamate has been assigned the trade mark Striatran by Merck and Co., Inc.

volunteer to serve as paid subjects in an experiment on effects of several drugs that improve work performance. They were further told that they would be asked to perform two types of tasks: first, those that simulated ordinary day-to-day activities, and second, a number of tests given under difficult and unpleasant conditions. It was felt that this structuring of their task was needed to reduce inter-subject variability in perception of and reaction to the drug treatments, the stressors, and the tests. Volunteers were asked to fill out a short "medical check-list," on which they were asked to check the frequency of occurrence of a variety of psychosomatic symptoms.

All drug treatments were administered one hour before the start of testing. Test sessions took between one and one and one-half hours. Drug treatments were as follows: 1) 400 mg. of emylcamate; 2) 800 mg. of emylcamate; 3) 800 mg. of meprobamate; 4) placebo. Meprobamate was employed as a comparison drug, because of possible similarity of effects and because of the many data already collected in previous studies as to the effects of meprobamate on the behavioral toxicity battery (Marquis *et al.*[4], 1957; Kelly *et al.*[1], 1958; Uhr, Pollard and Miller[6], 1959). Investigations by others had suggested that emylcamate was roughly twice as potent as meprobamate. Thus dose levels were chosen to be approximately 2 and 4 times the normal prescribed treatment, equivalent to 800 and 1600 mg. of meprobamate.

BEHAVIORAL TOXICITY TEST BATTERY. Eighteen objectively measured variables were scored from the various aspects of the patient's performance on the behavioral toxicity test battery.

A. *Driver Test* (7 scores). The American Automobile Association's "Auto Trainer" was used to test complex psychomotor skills, of the sort used while driving an automobile. The subject operates the trainer by sitting at and working the controls of a conventional shift automobile. A wide belt about 10 feet long, painted to resemble a winding road, extends in front of the control unit. A model car, connected to the steering wheel operated by the subject, rides on the belt. The subject's job is to keep the car on the road and to brake the car whenever a red light appears. For a more complete description of this apparatus see Marquis *et al.*[4] (1957).

Subjects were given trials as follows: 20 revolutions of the belt at a fixed low speed; 20 at a fixed high speed; and 20 at a speed controlled by the patient. Six reaction-time determinations were interspersed irregularly through the first 2 trials.

Accuracy, or proficiency, of driving in this situation is measured in terms of the subject's ability to keep the car on the road. Three accuracy scores were obtained: at the fixed low speed, at the fixed high speed, and at a variable speed, controlled by the subject. A "speed" score was also obtained: the time required for the trial when the subject was controlling his own speed. During this phase of the test the subject was told to drive as rapidly and as accurately as he could. A derived score was also computed—the ratio of the difference between the accuracy score at low fixed speed and the accuracy score at subject-controlled speed, divided by the time score. This speed-accuracy ratio, which indicated the degree to which speed was sacrificed for accuracy, or vice versa, may be interpreted as a measure of judgment. The 7 scores on the Driver Test thus included 3 accuracy scores, one speed score, one judgment score, and 2 reaction time scores.

B. *Vision Tests* (8 scores). Tests of various components of vision that might be affected by psychoactive drugs were conducted on the Bausch and Lomb master model Ortho-rater. This is an instrument designed to control illumination, distance, and presentation of visual stimuli (Marquis *et al.*[4], 1957).

Acuity was determined for both far and near vision; depth perception was determined for distant vision only. Vertical and lateral phorias for both near and far vision were also measured. Phoria scores indicate the relative posture or muscular balance of the eyes in relation to each other under conditions of controlled accommodation. A perfect vertical phoria score indicates that the horizontal midline in both the right and left visual fields is in the same axis. A perfect lateral phoria score indicates the same for the vertical midline.

C. *Steadiness Test* (3 scores). The subject was given practice and then asked to hold, in a standard manner, wrist on the table, a metal stylus, 3/32″ in diameter, in a hole in a metal Whipple steadiness board for a 15-second period, without touching the sides of the hole. Touching the metal sides activated an electronic counter, which summed duration of contacts in units of centiseconds, during the 15-second period. Three determinations of steadiness were made: for a 5/32″, a 4/32″, and a 3/32″ hole (Marquis *et al.*[4], 1957).

Results. Table 1 presents the results obtained from the variables scored on

the behavioral toxicity battery. This table shows the mean performance on each variable under each of the 4 drug treatments.

The difference between the mean performance of subjects under the influence of one drug and their mean performance under the influence of a second drug gives the estimate of the magnitude of the difference in effects between these two treatments. When this difference is evaluated in terms of the standard error of the difference (which is the best statistical estimate of the amount by which these means might differ as a result of chance alone), the statistical significance of this difference is found. This gives the probability that the change in performance is a dependable one, resulting from the difference between the effects of the 2 drugs, and not the result of

TABLE 1.—MEAN PERFORMANCE ON BEHAVIORAL TOXICITY BATTERY

	Drug Treatment			
Behavioral Test	*Emylcamate (800 mg.)*	*Emylcamate (400 mg.)*	*Placebo*	*Meprobamate (800 mg.)*
A. *Driving Test:*				
1. Slow-Accuracy (Hits)	262.5	263.3	264.4	257.0
2. Slow-Reaction (Time—10ths of seconds)	26.1	25.5	24.5	25.5
3. Fast-Accuracy (Hits)	197.6	194.8	201.0	190.0
4. Fast-Reaction (Time)	25.9	25.1	24.5	25.8
5. Variable-Accuracy (Hits)	186.0	185.9	184.4	176.2
6. Variable-Time	234.0	239.0	231.0	235.0
7. Judgment	0.006	0.006	0.006	0.006
B. *Orthorater (Vision):*				
8. Far-Acuity	10.3	10.5	10.3	10.2
9. Far-Lateral Phoria (Deviation)	1.9	2.2	1.9	1.9
10. Far-Vertical Phoria (Deviation)	0.6	0.8	0.8	0.8
11. Near-Acuity	10.1	10.2	10.2	10.2
12. Near-Lateral Phoria (Deviation)	2.5	2.9	2.8	2.4
13. Near-Vertical Phoria (Deviation)	0.9	1.0	1.0	0.8
14. Far-Depth Perception	4.1	4 0	4.3	4.2
15. Color Perception	3.7	3.6	3.6	3.7
C. *Steadiness (Seconds touched):*				
16. 5/32″ Hole	1.90	1.49	1.78	1.78
17. 4/32″ Hole	3.44	3.18	3.68	4.46
18. 3/32″ Hole	10.86	11.60	13.91	10.58

chance. Table 2 presents this evaluation. Mean differences are listed for each combination of the 4 drug treatments for each variable.

A small number of significant differences would be expected to occur as a result of chance alone in a study of this sort. When one hundred tests of significance are made, chance would account for one being significant at the 1% level, and 5 at the 5% level. Thus, with 18 variables and 6 treatment combinations, about one significance at the 1% level in the entire group of 108 significance tests and about one significance at the 5% level in each of the 18 tests for a combination of treatments, would be expected merely by chance. The number of significant effects found in the present study (2 at the 1% level and 9 at the 5% level, when 1.1 at the 1% level and 5.4 at the 5% level would be expected by chance alone) is not much greater than the prediction from random fluctuations.

On the other hand, the significant effects appear to cluster around a few related variables, so that it seems possible that they are indicative of real effects. Thus all but 2 of the signifi-

TABLE 2.—MEAN DIFFERENCE, AND SIGNIFICANCE OF DIFFERENCE, IN PERFORMANCE UNDER CONTRASTING DRUG TREATMENTS, ON THE BEHAVIORAL TOXICITY BATTERY

	Combination of Drug Treatments Contrasted (a positive score indicates better performance under the treatment listed first)					
Behavioral Test	*Emylcamate 800 mg. vs. Placebo*	*Emylcamate 400 mg. vs. Placebo*	*Meprobamate 800 mg. vs. Placebo*	*Emylcamate 800 mg. vs. Meprob.*	*Emylcamate 400 mg. vs. Meprob.*	*Emylcamate 800 mg. vs. 400 mg.*
A. *Driving Test:*						
1. Slow-Accuracy	−1.9	−1.1	− 7.4	5.5	6.3	−0.8
2. Slow-Reaction	−1.6†	−1.0	− 1.0*	−0.6	0.0	−0.6
3. Fast-Accuracy	−3.4	−6.2	−11.0*	7.6	4.8	2.8
4. Fast-Reaction	−1.4†	0.6	1.3	−0.1	0.7	−0.8*
5. Variable-Accuracy	1.6	1.5	− 8.2	9.8*	9.7	0.1
6. Variable-Time	3.0	8.0*	4.0	−1.0	4.0	−5.0
7. Judgment	no differences					
B. *Orthorater (Vision)*						
8. Far-Acuity	0.0	0.2	− 0.1	0.1	0.3*	−0.2
9. Lateral Phoria	0.0	−0.3	0.0	0.0	−0.3	0.3
10. Vertical Phoria	0.2	0.0	0.0	0.2	0.0	0.2*
11. Near-Acuity	0.0	0.1	0.1	−0.1	0.0	0.1
12. Lateral Phoria	0.3	−0.1	0.4	−0.1	−0.5	0.4
13. Vertical Phoria	0.1	0.0	0.2	−0.1	−0.2	0.1
14. Depth Perception (Far)	−0.2	−0.3	− 0.1	0.1	−0.2	0.1
15. Color Perception	0.1	0.0	0.1	0.0	−0.1	0.1
C. *Steadiness*						
16. 5/32″ Hole	−0.12	0.29	0.00	−0.12	0.29	−0.41
17. 4/32″ Hole	0.24	0.50	0.78	1.02	1.28	−0.26
18. 3/32″ Hole	3.05	2.31	3.33	−0.28	−1.02	0.74

*Difference significant beyond the 5% level.
†Difference significant beyond the 1% level.

cant effects were found on the 7 performance scores from the driving test. And, further, these effects appear to indicate a consistent pattern.

The large, 800-mg. dose of emylcamate, in contrast to the placebo, led to a significant (1% level) slowing of chose to drive, was significantly slower (5% level) for 400 mg. of emylcamate than for placebo, a possible indication of greater caution under the influence of the drug. The general consistency of these effects is more apparent when nonsignificant trends from similar tests

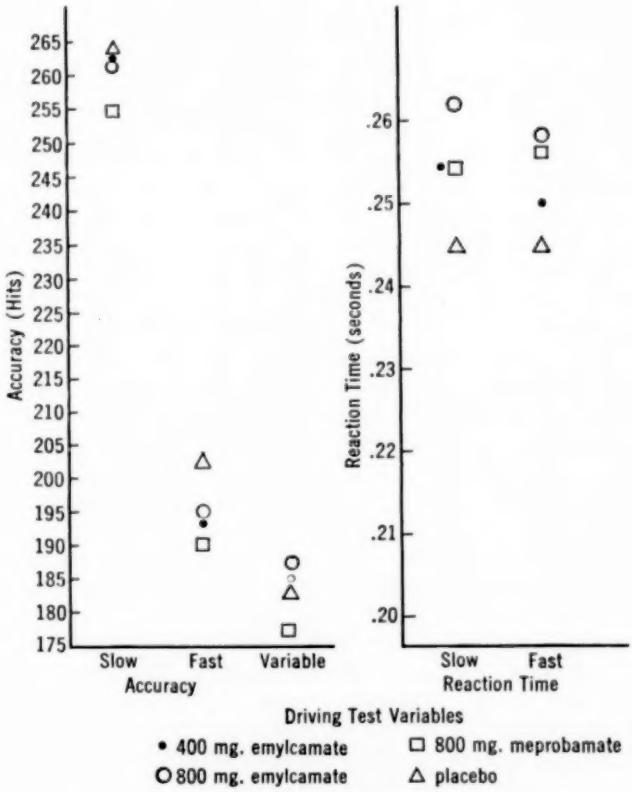

Fig. 1.—Accuracy and reaction time on the driving test.

brake reaction time on both reaction time determinations, at slow and at fast speed. The 400-mg. dose of emylcamate did not have this effect, and in fact also produced significantly better reactions (5% level) at fast speed than did the 800-mg. dose. The time score at variable speed, which gives a measure of the rate at which the subject can be viewed in conjunction with the significant effects, as in Fig. 1.

As contrasted with 800 mg. of emylcamate, 800 mg. of meprobamate appears to have significant but lesser effects in slowing reaction time. It also has significant effects in lowering accuracy in keeping the car on the road, whereas emylcamate had no adverse ef-

fects on this aspect of driving. Thus 800 mg. of emylcamate led to significantly greater accuracy (5% level) at variable speed than did meprobamate. Meprobamate led to significantly poorer (5% level) reaction times at slow speed and poorer accuracy at fast speed than did placebo, while 800 mg. of emylcamate produced significantly poorer (1% level) reaction times at both slow and fast speeds.

Of the 66 statistical tests made on the Orthorater and the steadiness test, only 2 were significant beyond the 5% level, whereas 3.2 would be expected by chance alone. There appears to be little reason to conclude, without additional evidence from a replication of these parts of the experiment, that they are indicative of anything other than random fluctuations.

Discussion. This is the fourth in a series of studies in which the effects of meprobamate, as compared with placebo, were examined on the driving test, Orthorater, and steadiness test. The first two studies did not find any significant effects either of a single 800-mg. dose (Marquis *et al.*[4], 1957) or under one month of continuous 800-mg. treatment, b.i.d. (Kelly *et al.*[1], 1958). Both of these studies tested drug effects on normal subjects. The third study, of chronic effects on anxious subjects (Uhr, Pollard and Miller[6], 1959) gave indications of results similar to those found in the present experiment. Thus there appears to be a certain consistency of results emerging as to the effects of meprobamate. Other laboratories have reported similar effects: of slowing on simple reaction time and psychomotor tasks (Kornetsky[2], 1958), and decrements in performance on simulated driving (Loomis and West[3], 1958). The picture, then, one that appears to be reinforced by the results of the present experiment, is one of slight, but consistent, slowing in reaction and decrease in accuracy when both these functions are called for simultaneously, as on the complex driving test. We have found these effects only with doses of 800 mg. or more, twice the recommended clinical dose of meprobamate, the usual clinical dose producing no behavioral toxicity by our tests. The slight differences in findings between our studies can probably be explained by the different populations used and statistical variation.

The 800-mg. dose of emylcamate appears to slow the reaction time slightly more than a similar dose of meprobamate. But it does not lead to a consistent decrease in accuracy, and it may be allowing the subject to make better use of his own judgment as to his condition than does meprobamate. The 400-mg. dose of emylcamate, the dose that is probably most nearly comparable in clinical potency to 800 mg. of meprobamate, does not appear to have any of the slowing effects of either the larger 800-mg. dose of emylcamate or 800 mg. of meprobamate.

The practical importance of the effects of these drug treatments raises a further question that is completely unrelated to the significance of the existence of these effects. In terms of percentages, all of these decrements are small. They are probably far smaller than the differences in driving ability and performance from one driver to the next, or even, for the same driver, from a good to a bad day. Their effects on the margin of safety in driving must be assessed from other types of experiments. It seems likely that anything that affects performance will under some circumstance lower performance that is barely above a critical level to the danger point. On the other hand, this may be an extremely rare occurrence. And the effects of psychoactive drugs may be far milder than the ef-

fects of many of the day-to-day experiences (such as amount of sleep, diet, or changes in mood) that normally are never considered threats to proper driving or machine operation.

Summary. The effects of single doses of 800 mg. of emylcamate, 400 mg. of emylcamate, 800 mg. of meprobamate, and matching placebos were tested on a behavioral toxicity battery with 18 variables. Forty-nine normal male subjects were pretrained and tested under all of the 4 drug treatments, according to a double-blind and counterbalanced design, each subject acting as his own control.

Seven determinations of reaction time, accuracy and preferred speed were made on the driving test; 8 measures of visual functions were made on the Orthorater; and 3 determinations of steadiness were made on the Whipple Steadiness Board. As compared with placebo, 800 mg. of emylcamate, well above the recommended single clinical dose, led to significantly slower reaction times, whereas 400 mg. of emylcamate did not. Neither dose had any consistent effect upon accuracy, and 400 mg. of emylcamate increased caution in trading off speed for accuracy. Meprobamate, in 800-mg. doses (double the usual clinical dose and roughly equivalent in clinical effects to 400 mg. of emylcamate) led to both a slowing of reaction time and a decrease in accuracy. The 800-mg. dose of both drugs appeared to have some effect on components of psychomotor behavior related to driving: emylcamate chiefly on reaction time, meprobamate a less specific effect on both reactions and accuracy. Explanations for apparent inconsistency of these findings about meprobamate with previous studies are given. No behavioral toxicity has been found by our tests for dosages of meprobamate less than 800 mg., 400 mg. being the usual single clinical dose.

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(Interlingua on page 162)

EXPERIMENTALLY DETERMINED EFFECTS OF EMYLCAMATE (STRIATRAN) ON PERFORMANCE, AUTONOMIC RESPONSE, AND SUBJECTIVE REACTIONS UNDER STRESS

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The present paper compares the effects of emylcamate*, of meprobamate, and of placebo on various behavioral, autonomic, and subjective measures on subjects under experimentally produced stress.

Procedure. We examined the acute effects of two dose levels of emylcamate (400 mg. and 800 mg.), of 800 mg. of meprobamate, and of matching placebo, in a double-blind, crossover design. Each subject served as his own control. Forty-nine normal paid volunteers, inmates at the State Prison of Southern Michigan, served as subjects. The details of the design have been given in a previous paper (Uhr and Miller[1,2], 1959) on another aspect of this overall research. The aspect reported on in the present paper concerns the results of our administering to this population of subjects a wide variety of short tests under stress.

STRESS SITUATION. The stress situation consisted of a number of physical discomforts and tension-producing stimuli presented to the subject while he sat in the "stress box" and worked at his tasks. The "stress box" was built to confine the subject in a space small enough to give some feeling of being cramped and oppressively contained. It also gave the subject the impression of being cut off, in a small cubicle, from the larger outer environment. It was designed to follow, in general conception (although with major modifications) the physical situation in which subjects were tested in experiments reported by Gorham and Orr[2,3] (1957, 1958). The subject sat at a long narrow table and the box was lowered over his head, around him and a portion of the table. The box was 36″ wide, 36″ deep and rose 30″ over the 30″ table.

Positioning of the subject consisted in a standard procedure designed to familiarize him with his task, to make salient to him and prepare him for the physical stressors. First, during the pretraining session, the subject was shown the box and told that it was designed to simulate the uncomfortable, difficult, and tension-provoking situations under which people in military service and other difficult jobs often must work. The subject was told that he would work while being subjected to the effects of occasional blasts of compressed gas (CO_2), loud noises, and high voltage shocks. Earphones, a fine nozzle tube, and shock electrodes were pointed out to him. He was shown a climbing "Jacob's ladder" arrangement of metal bar electrodes positioned

*In the United States, emylcamate has been assigned the trade mark Striatran by Merck and Co., Inc.

in front and slightly to the left of his face. He was told that he would see intermittent rising sparks (reaching 2 to 3 inches in length) between these bars. Also he was informed that the sparks would occur along with the shocks he received, and were in fact a part of the high voltage circuit used to generate the shocks. Moreover he was told that the small pane of mirror glass directly in front of his face was a one-way window through which the tester would be observing his work and his reactions to stress. Finally, he was examined for shock sensitivity. Over Offner electrode paste, the electrodes (Caholby 3 cm. piece of stainless steel) were placed on the left forearm (one about 2 inches directly above the other), and strapped on with surgical bandage. On the pretest day, feeling threshold was determined by a series of ascending shocks. Then the subject was given one shock, toward the high end of the range of shocks to be used in the experiment proper. He was told that this was a relatively weak example of what he would receive, and that shock level would be varied, but always kept within the limits of safety, as established by our own and many other previous experiments. The shocker used was built in our laboratory. A 60-cycle Schmitt trigger was differentiated to give an exponential decay to zero within one millisecond. Peak voltage used in experimental sessions ranged between 48 and 74 volts. Average current was well within the range of safety, as reported by Dalziel[1] (1956). Shock was presented irregularly, five presentations during each 60″ physical stress period (designated by a "red light" signal to the subject). The duration of individual shocks ranged from 2 to 4 seconds. Shock level was changed systematically in an attempt to counteract the inevitable adaptation effects. This was done according to the following schedule: Four shock levels were established as the range of shock to be used throughout the experiment. These were 1) 48 volts, 2) 54 volts, 3) 66 volts, 4) 74 volts. Each of the 4 experimental sessions was divided into thirds. Thus, on the first day, subjects started at 48 volts, and were raised in two steps to 54 and 66 volts. On the second experimental day, the same levels were used. On the third day, experimenting began at the 54 volt level, and was raised according to the same standard procedure to 66 and 74 volts. On the fourth day the levels remained the same as the third day. As equivalent subjective shock was the goal of standardization, the experimenter made adjustments in this procedure (chiefly, by not raising base shock levels on the third day), when he had clear evidence that the subject was undergoing a great deal of discomfort from the shock. The level was not raised for 6 subjects. (The exact times at which shock voltage levels were raised will be indicated during the description of tests used.)

The "Jacob's ladder" was made of two ¼″ stainless steel rods, 9½″ long, angled up from a starting gap of 1″ to a final gap of 3″. It was activated by the same relays that activated the shocking circuit, and was powered by a Welch high voltage induction coil (#2391A). Gas blasts from tanks of compressed carbon dioxide, regulated to 25 lbs. per square inch pressure, were directed through ¼″ rubber tubing and a ⅛″ metal nozzle in front of the subject, a sharp stream of gas hitting his forehead or the side of his face. During the one-minute physical stress session, the subject received 3 irregularly spaced air blasts, of 1-second to 3½-second duration. Noise was fed to the subject through earphones connected to a Gray Audograph. The Audograph disks were cut from noises

produced by 2 laboratory audio oscillators. Noises were made intermittent, changing in frequency, intensity, and duration in an attempt to eliminate any adaptation effects.

One-minute "physical stress" (red light) and "threat of stress" (green light) periods were presented in pairs. Physical stress came first, then threat of stress, for the first 3 tests. For the last 5 tests, threat of stress came first and physical stress second. Thus 8 short behavioral tests were given once during each of the 2 types of stress periods, according to a regular schedule. The ordering of tests was held constant throughout the experiment. Several alternate test forms were used for tasks on which familiarity with an item might improve performance. The presentation of these forms was varied across the physical stress and threat of stress periods, and across the 4 experimental sessions, and balanced out across subjects. Autonomic stress effects and subjective reactions were also measured, or described below.

ATTENTION TEST. *Behavioral Tests.* The first test administered to subjects consisted of a list of 12-letter "words," each composed from a random number table. The subject's job was to check those "words" in which the key letter, "E," occurred. This test, adapted from Primac, Mirsky and Rosvold[10] (1957), is more fully described in Kelly, Miller, Marquis, Gerard and Uhr[6] (1958). It has been used as a quick check of continuing attention. During this test, the subject was presented with a second task, designed to divide his attention. Directly in front of his face, so that he could be aware of its light by a minimal shift of his eye, was a lighted "nixie" tube. This is a 1″ neon-bulb like tube in which the digits 0 through 9 are wired, so that any single digit number can be switched on and presented as a stimulus. The subject was told that this bulb would always be lighted with a number, and that, when the number changed, he was to write down the sum of the new and the old number. The number was changed 4 times, at irregularly spaced intervals, during each of the 2 one-minute test periods.

Addition-Subtraction. The subject was presented with simple one-digit columns of 2 numbers, with the instructions to add together those columns in which the second (lower) number was greater than the first, but to subtract the second number from the first when it was equal to or less than the first. This need to hold in mind a guiding rule, which in turn would change the subject's set for the problem, was introduced in an attempt to increase the stress-sensitive dimensions of complexity and adaptability in the task, as suggested by Horvath[5] (1959).

Subtract 17's. The subject was told to subtract successive 17's from a number told to him orally by the experimenter, at the start of each test period. He was also given a 6-digit number by the experimenter, and told that he would be asked to remember it during the one-minute period, and to write it down on his test sheet at the end of the period. This test was the first under the second, or raised, shock condition.

Reaction Time. A 4-choice (two bit) reaction time experiment was simulated in paper-and-pencil form by means of a "musical staff" of 5 lines, giving 4 horizontal spaces between lines, in which target "O's" were placed, according to a random number table. The subject's job was to work as fast as he could through the successive stimuli, crossing out the number, in columns directly below the staff, that corresponded to the "O" in that column. The staff spaces were numbered "1, 2, 3, 4," while the num-

bers to be crossed out were placed "4, 3, 2, 1," so that a reversal in coding was necessitated. For this and all subsequent tests, the threat of stress period came first.

Tracking. The subject was asked to draw a smooth, continuous line through successive, irregularly placed gaps in rows of parallel lines, moving back and forth, to right and left, across the page. This test was adapted from the MacQuarrie Tests for Mechanical Ability, Tracing Subtests. The physical stress period for this test was the first under the third final level of shock.

Word Productivity. The subject was asked to write all the words he could think of beginning with a specified letter (letters chosen for equivalent frequency).

Bourdon Attention and Alternate Set Test. During the first of 4 one-minute test sessions, the subject was asked to draw a vertical line through clumps of 3 dots, a horizontal line through clumps of 4 dots, and no line through clumps of 5 dots. During the second period, he was asked to follow a new set of directions—vertical through 3, none through 4, and horizontal through 5. During the third and fourth periods (one under each stress situation) he was asked to alternate his processing method, between the first and the second, changing at the points indicated on the test sheet (every 10 stimuli). This followed closely the procedure previously reported by Miller and Uhr[8] (1959) in experiments on drug effects. Before the last 2 test sessions, the subject was presented with 6-digit numbers to be written down at the end of the period, according to the procedure used during the "Subtract 17" testing. The 2-digit span presentations were combined for analysis as a single score.

AUTONOMIC TESTS. *Galvanic Skin Resistance.* A microammeter, connected to the electrodes used for the electric shock, was used for 4 determinations of baseline skin resistance. The experimenter could throw a switch to read skin resistance at any time during the experiment. Four readings were recorded: 1) before stress, 2) after the first one-minute physical stress period, 3) after the third physical stress period (the first at the second, raised, shock level) and 4) after the last physical stress period.

TESTS OF SUBJECTIVE REACTIONS. After the last behavioral test performed under physical stress, the subject was asked to report on his subjective reactions to the stress situation on several standardized rating schedules as follows:

Semantic Differential. The subject was asked to rate his present feelings on a number of scales that have been found by Osgood[9] (1952) to form 3 factors of semantic meaning: activity, potency, and evaluative. The modification used was first reported by Kelly, Miller, Marquis, Gerard, and Uhr[6] (1958).

Self-Report Scales. Subjects were asked to rate themselves on 7 scales describing how they felt at the present time. These included 3 ratings of their physiological state: how good, tense, and alert they felt. The final 4 scales asked about their psychological state: how confident, good, tense, and anxious they felt (Kelly, Miller, Marquis, Gerard, and Uhr[6] 1958).

Results. Table 1 presents a summary view of the results obtained in the entire study, including the behavioral toxicity phase of the experiment, as reported by Uhr and Miller[12] (1959). The tests have been divided into 7 major types: From the first phase, 1) psychomotor performance on the driving test, 2) visual abilities on the orthorater, 3) steadiness; from the second phase, 4) behavioral test performance

under physical stress, 5) behavioral test performance under threat of stress, 6) autonomic response to stress on the psychogalvanometer, and 7) self-reported reactions to stress. Within each type, the number of statistically significant drug effects is listed, for all 6 combinations of the 4 drug treatments lumped together. This gives an overall picture that allows for a comparison between the number of sigificant differences obtained in this experiment and the number that would be expected by chance alone. When a large number of statistical tests is made, 5% of them will be "significant" at the 5% level and 1% at the 1% level merely as a result of chance.

From Table 1 it is clear that the only behavioral toxicity tests that showed differences in effects of the different drug treatments examined were those on the driver trainer (1). Of the measures of stress effects, only the autonomic responses during stress (6) and subjective reactions as reported immediately after stress (7) were sensitive to differences in drug effects. Because of the large number of variables tested in this study, only results for these 2 types of tests will be examined in detail, since the effects on performance on the behavioral tests were almost certainly the results of mere chance.

Table 2 presents the mean scores on each autonomic and self-report variable under each of the 4 drug treatments.

TABLE 1.—THE NUMBER OF CONTRASTS BETWEEN COMBINATIONS OF TWO DRUG TREATMENTS FOUND SIGNIFICANT AT THE 5% LEVEL, FOR EACH OF THE SEVEN TYPES OF TESTS ADMINISTERED

Tests:	*Number of Contrasts:*		
	Tested for Significance	*Found Significant*	*Expected Significant by Chance Alone**
A. *Behavioral Toxicity Battery*			
1. Driving tests	42	7	2.1
2. Vision tests	48	2	2.4
3. Steadiness test	18	0	0.9
B. *Stress Measures*			
4. Performance under physical stress	60	1	3.0
5. Performance under threat of stress	60	1	3.0
6. Baseline galvanic skin resistance	24	10	1.2
7. Subjective reactions	60	7	3.0
Total	312	28	15.6

*This probably tends to be an underestimate, because of interdependencies between behavioral variables scored and between drug combinations examined.

Table 3 presents the mean differences between all combinations of the drug treatments, taken 2 at a time. Significant differences are starred. Critical ratios greater than 1.96, significant at the 5% level, are indicated by one star (*). Those greater than 2.54, significant at the 1% level, are indicated by a dagger (†).

Meprobamate, as contrasted with all other treatments, gave consistently higher galvanic skin resistances during the entire stress session. Neither dose level of emylcamate was significantly different from placebo. The 800-mg. dose of emylcamate and the 800-mg. dose of meprobamate led to signifi-

cantly lower feelings of activity than placebo. The 800-mg. dose of emylcamate produced feelings of greater calmness (less anxiety) and greater relaxation (less tenseness) than both placebo and meprobamate. On the calm-anxious scale, the 800-mg. dose of emylcamate led to feelings of greater calmness than did the smaller 400-mg. dose of emylcamate.

jective effects were examined by means of an empirically validated test, the semantic differential, and self-report scales. Before the research began we had suggested that the behavioral tests would be the most sensitive in the stress situation to drug effects. The results were in sharp contrast, showing no effects on performance, but several effects on both autonomic and subjective reactions.

TABLE 2.—MEAN SCORES ON AUTONOMIC MEASURES AND SELF-REPORT SCALES

Variable: *Galvanic Skin Resistance* (ohms)	*Drug Treatment*			
	Emylcamate 800 mg.	*Emylcamate 400 mg.*	*Placebo*	*Meprobamate 800 mg.*
1. First reading	49,500	47,318	42,373	74,629
2. Second reading	25,961	26,408	22,796	34,722
3. Third reading	17,261	19,181	16,411	21,186
4. Fourth reading	13,204	13,146	13,636	15,384
Subjective Reports				
Semantic Differential				
5. Activity	13.7	13.9	14.8	13.9
6. Potency	13.0	12.8	13.2	12.9
7. Self-Evaluation	14.1	14.0	13.8	13.9
Self-Report Scales				
8. Physical—Good	5.3	5.4	5.5	5.5
9. Physical—Tense	4.1	4.4	4.5	4.6
10. Physical—Alert	4.7	4.5	4.8	4.8
11. Psychological—Confident	5.1	5.0	4.8	4.8
12. Psychological—Anxious	2.0	2.8	3.1	2.8
13. Psychological—Tense	3.8	4.3	4.5	4.4
14. Psychological—Good	5.3	4.9	5.2	5.3

Discussion. Three levels of stress reactions were tapped in this experiment. Performance was measured on short behavioral tests of simple arithmetic, fluency, adaptability and psychomotor skills. Autonomic reactions were measured on the psychogalvanometer. Subjective effects were examined by means of an empirically validated test, the semantic differential, and self-report scales. Before the research began we had suggested that the behavioral tests would be the most sensitive in the stress situation to drug effects. The results were in sharp contrast, showing no effects on performance, but several effects on both autonomic and subjective reactions.

It is of course quite likely in a stress situation that the subject will mobilize his reserves and attempt to compensate for and overcome the handicaps imposed upon him. This appears to have been the case in the present ex-

periment. Possibly prisoner subjects were better able than typical college student subjects to cope with the stressful situation. They may even have responded to it as a challenge (as in fact was indicated by several of our subjects). The repetition of the stress situation for 4 different test sessions may also have given the subjects enough time to learn to compensate more effectively.

The high levels of skin resistance under the effects of meprobamate, as contrasted with both placebo and emylcamate, is consistent with the findings of Laties[7] (1957) as to meprobamate's effects. The lowered feeling of activity, under both meprobamate

TABLE 3.—MEAN DIFFERENCES, AND SIGNIFICANCE OF DIFFERENCES, IN SCORES UNDER CONTRASTING DRUG TREATMENTS ON AUTONOMIC MEASURES AND SELF-REPORT SCALES

	Combination of Drug Treatments Contrasted (a plus sign indicates better score under the treatment listed first)					
Variable: *Galvanic Skin Resistance*	*Emylcamate 800 mg. vs. Placebo*	*Emylcamate 400 mg. vs. Placebo*	*Meprobamate 800 mg. vs. Placebo*	*Emylcamate 800 mg. vs. Meprob.*	*Emylcamate 400 mg. vs. Meprob.*	*Emylcamate 800 mg. vs. 400 mg.*
1. First reading	7,127	4,945	32,256†	−25,129†	−27,311*	2,182
2. Second reading	3,155	3,612	11,926†	−8,771*	−8,314*	−457
3. Third reading	850	2,770	4,775*	3,925*	−2,005	−1,920
4. Fourth reading	−432	−490	1,748	−2,180*	−2,238*	58
Subjective reports						
Semantic Differential						
5. Activity	−1.1*	−0.9	−0.9*	−0.2	0.0	−0.2
6. Potency	−0.2	−0.4	−0.3	0.1	−0.1	0.2
7. Self-Evaluation	0.3	−0.2	0.1	0.2	0.1	0.1
Self-Report Scales						
8. Physical—Good	−0.2	−0.1	0.0	−0.2	−0.1	−0.1
9. Physical—Tense	0.4	0.1	−0.1	0.5	0.2	0.3
10. Physical—Alert	−0.1	−0.3	0.0	−0.1	−0.3	0.2
11. Psychological—Confident	0.3	0.2	0.0	0.3	0.2	0.1
12. Psychological—Anxious	1.1†	0.3	0.3	0.8†	0.0	0.8†
13. Psychological—Tense	0.7*	−0.2	−0.1	0.6*	−0.1	0.5
14. Phychological—Good	0.1	−0.3	0.1	0.0	−0.4	0.4

*Difference significant beyond the 5% level
†Difference significant beyond the 1% level

and emylcamate, is consistent with the slight slowing effect found on the driving test. It is also consistent with the results obtained by Uhr, Pollard, and Miller[13] (1959) in a study of meprobamate's effects on anxious subjects. The subjective reactions of calmness and relaxation as a result of the 800-mg. dose of emylcamate would seem to indicate a real feeling of "tranquility" under stress as a result of this drug.

Summary. The effects of single doses of 800 mg. of emylcamate, 400 mg. of emylcamate, 800 mg. of meprobamate, and matching placebos were evaluated on a number of measures testing stress reactions. Forty-nine normal male volunteer subjects were pretrained and tested under all 4 drug treatments, according to a double-blind and counterbalanced design, each subject serving as his own control.

Subjects were tested while working in a stressful situation that included random shocks, noise and airblasts. These were presented to the subject while he sat in a small box and performed a variety of simple behavioral tests. One-minute physical stress periods were interspersed with one-minute threat of stress periods. All tests were taken, on matched forms, under both types of stress. Autonomic reactions were assessed by means of 4 determinations of galvanic skin resistance during the stress session. Subjective reactions to the stress were determined by means of a number of self-ratings.

Contrary to expectations, no drug effects were found on performance under either physical stress or threat of stress situations. Meprobamate had a consistent effect, in contrast to both emylcamate and to placebo, in raising galvanic skin resistance. Both meprobamate and emylcamate, in 800-mg. doses, led to feelings of less activity. The 800-mg. dose of emylcamate led to subjective feelings of greater calmness and relaxation than either meprobamate or placebo. The 400-mg. dose of emylcamate and the 800-mg. dose of meprobamate affected subjective anxiety to essentially the same degree.

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SUMMARIO IN INTERLINGUA

Determination Experimental del Effectos de Emylcamato (Striatran) Super le Performance, le Responsa Autonomic, e le Reactiones Subjective sub Conditiones Stressose

Esseva evalutate le effecto exercite per doses solitari de 800 mg de emylcamato, 400 mg de emylcamato, 800 mg de meprobamato, e de correspondente placebos super un numero de parametros usate pro testar reactiones a stress. Quarantanovem normal voluntarios mascule esseva pretrainate e testate sub le influentia del 4 medicationes secundo un systema bis-occulte e contrabalanciate in le qual cata subjecto serviva como su proprie subjecto de controlo.

Le subjectos esseva testate durante que illes laborava in un situation stressose que includeva—distribuite al hasardo—choc, ruito, e jectatas de aere. Istos esseva presentate al subjecto durante que ille sedeva in un micre cassa e executava un varietate de simple tests de comportamento. Periodos de un minuta de stress physic esseva alternate con periodos de un minuta de menacia de stress. Omne tests (o tests equivalente) esseva repetite sub ambe typos de stress. Reactiones autonome esseva evalutate per medio de quatro determinationes del resistentia galvanic del pelle durante le periodo de stress. Reactiones subjective al stress esseva determinate per medio de un numero de auto-estimationes.

Per contrasto con le expectationes, nulle effectos del drogas esseva detegite super performance in situationes de stress physic o de menacia de stress. Meprobamato habeva un effecto uniforme—per contrasto con emylcamato e etiam con le placebos—in elevar le resistentia galvanic del pelle. Meprobamato e etiam emylcamato, in doses de 800 mg, produceva le sensation de reducite activitate. Le dose de 800 mg de emylcamato produceva sensationes subjective de calma e relaxation plus grande que illos producite per meprobamato o per le placebos. Le dose de 400 mg de emylcamato e le dose de 800 mg de meprobamato afficeva le anxietate subjective in essentialmente le mesme grado.

THE STATUS OF THE ADRENAL GLAND IN THE ASTHMATIC PATIENT

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The effectiveness of corticosteroids and corticotropin in the patient with acute or chronic airway obstruction has been well documented. The question is whether or not the effect of the steroids in such cases is dependent on an adrenal cortical insufficiency.

Siegel *et al.*[20] detected a marked increase in circulating corticosteroids in one of his patients (terminal, in *status asthmaticus*) and concluded that there was no adrenocortical insufficiency. Nelson and Samuels[12] suggested that a lowering of utilization in the liver causes the preterminal rise in the blood 17-hydroxycorticosteroids. Burrage[4], on the other hand, measured the urinary 17-ketosteroid excretion in asthmatic individuals before and after ACTH stimulation, and felt that the increase in the excretion rate was of a low order.

Since 1955, 52 adult patients have been studied at National Jewish Hospital at Denver, Colorado, as part of a pilot study on asthma. In addition to a clinical evaluation of the effect of separating adults from their customary environments, biochemical studies were undertaken to determine the status of the adrenal gland in the asthmatic patient. The purpose of this report is to describe results of studies aimed at answering the following questions: 1) What is the urinary corticoid response to ACTH stimulation in asthmatics who never received steroid therapy? 2) Does treating an asthmatic with corticosteroids alter the urinary corticoid response to subsequent ACTH stimulation? 3) Is there any difference in the urinary corticoid response to ACTH when the asthmatic has already received both corticosteroid and intermittent ACTH therapy?

Methods and Materials. Nineteen hospitalized adult patients with inactive pulmonary tuberculosis were selected as controls for comparison with the experimental group of 52 asthmatic patients aged 15 to 65 years. Beginning at 9:00 A.M., urine was collected for a 24-hour period and the total 17-ketosteroid and the 17-hydroxcorticosteroid excretion was determined by the Zimmerman reaction and the Reddy method (Sobel *et al.*[22], Reddy, Jenkins and Thorn[15], and Reddy[14]) respectively. The next day, 20 USP units of ACTH in 500 ml. of 5% dextrose solution were infused during an 8-hour period, and another 24-hour urine specimen was collected, as before. The creatinine content was calculated for each of these 24-hour urine samples to insure the completeness of collection.

The patients were divided into 5 groups: 1) Controls (C). 2) Asthmatics* who had

*For the purpose of this study, an asthmatic patient was defined as an individual who had an established history of cutaneous or clinical allergic reactions and who was experiencing paroxysmal episodes of airway obstruction manifested by wheezing and dyspnea, which could not be attributed to any other clinical condition.

TABLE 1.—CHANGES IN THE 24-HOUR URINARY 17-HYDROXYCORTICOSTEROID EXCRETION BEFORE AND AFTER ACTH STIMULATION

	Group C		*Group NS*		*Group PS*		*Group SO*		*Group B*	
Index	*Before ACTH mg./24 hr.*	*Difference in mg./24 hr. after ACTH*	*Before ACTH mg./24 hr.*	*Difference in mg./24 hr. after ACTH*	*Before ACTH mg./24 hr.*	*Difference in mg./24 hr. after ACTH*	*Before ACTH mg./24 hr.*	*Difference in mg./24 hr. after ACTH*	*Before ACTH mg./24 hr.*	*Difference in mg./24 hr after ACTH*
Mean	6.16	10.53	5.19	8.35	7.27	8.42	5.7	8.51	5.8	12.02
Standard Error	.58	1.24	.58	1.68	.96	2.70	1.73	1.71	.97	1.87
Range	3.1–11.4	1.3–24.1	1.9–10.4	.2–27.2	1.1–13.3	—3.00–29.7	0.5–21.8	.5–17.7	1.3–13.3	.7–25.0
Number of Patients	19	19	17	17	12	12	11	11	12	12
Number of Tests	19	19	17	17	12	12	11	11	12	12

(C) Control patients.
(NS) Asthmatics who had never before received corticosteroids.
(PS) Asthmatics who had not received corticosteroids for ½ to 14 months (mean 5 months).
(SO) Asthmatics who were receiving only corticosteroids at the time of the study.
(B) Asthmatics who had received both corticosteroids and intermittent corticosteroid therapy for 1 to 18 months (mean 6 months) prior to the study.

never received steroid therapy (NS). 3) Asthmatics who had not taken corticosteroids (PS) for 2 weeks to 14 months (mean 5 months). 4) Asthmatics who were receiving corticosteroids at the time of the corticotropin stimulation (SO)*. 5) Asthmatics who had received both corticosteroids and intermittent corticotropin therapy (B) prior to this study for 1 to 18 months (mean 6 months).

Henceforth the above groups will be referred to by their abbreviated symbols.

Because the changes in the 17-ketosteroid excretion rates paralleled those observed in the 17-hydroxycorticosteroid studies, only the latter data will be presented.

Since the mean for the control group (derived from the "Difference in mg. per 24 hours after ACTH," in Table 1) was similar to that obtained by Laidlaw *et al.*[10], in his normals following ACTH stimulation, it is assumed that our 19 patients with inactive pulmonary tuberculosis comprised a satisfactory control group.

Table 1 shows the ranges of urinary corticoid excretion rates before and again following ACTH stimulation in the groups C, NS, PS, SO, and B.

Using the *t*† test for unpaired variates, the means of each group, in terms of mg. per 24-hour urinary corticoid excretion, were compared.

Results. The means of each group, in terms of mg. per 24-hour urinary corticoid excretion before ACTH stimulation were compared (Table 1). Because the P (probability) values based upon the formula for unpaired data were all greater than .05 (the upper limit for a significant statistical difference between groups in a biological study), it appeared that all the patients studied could have come from the same population (Table 2).

*Eleven patients were studied in this group and the corticosteroid therapy in 7 of the patients was 8 mg. per day of 6-methyl, 1 delta hydrocortisone. Two patients received 4 mg. per day; and the other 2 received 12 and 16 mg. per day, respectively.

$$t\dagger = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{\Sigma i\,(x_i - \bar{x}_1)^2 + \Sigma i\,(x_{2i} - \bar{x}_2)^2}{N_1 + N_2 - 2}\left(\frac{1}{N_1} + \frac{1}{N_2}\right)}}$$

Where N_1 = size of sample 1

N_2 = size of sample 2

Similarly, the means of the difference in mg. per 24 hour between the initial and resultant rise in the urinary corticoid excretion in each group after ACTH stimulation were compared as shown in Table 1. The P values were again greater than .05 suggesting that the groups studied could have come from the same population (Table 3).

It was our impression that no significant statistical difference before or after exogenous ACTH stimulation had been demonstrated between the control group, the asthmatic patient not treated with steroids, and those asthmatic patients on corticosteroids at the time of the study or who had received corticosteroid or combined corticosteroid and intermittent corticotropin therapy prior to the study.

Discussion. In such instances where an adrenal carcinoma exists and where the gland is no longer controlled by the pituitary or responsive to exogenous ACTH, parenteral stimulation by ACTH may fail to provide evidence of adrenocortical activity in spite of the enormous amounts of steroids that the gland may be excreting (Burnett *et al.*[3]). For the vast majority of patients, however, the response to ACTH stimulation does afford a reliable index to adrenal cortical reserve and secretory capacity. Consequently, as suggested by Jenkins *et al.*[8], our results have been interpreted on an all-or-none basis.

There was no apparent difference between the asthmatic group never previously treated with steroids and the control group in their response to ACTH stimulation. Nor was capacity of the gland to respond to administered ACTH appreciably diminished, even when the patients had formerly been on corticosteroids. Likewise, combined intermittent ACTH therapy and corticosteroid therapy failed, in comparison with the other groups, to enhance

the responsiveness of the adrenal gland to ACTH. The present findings support the concept that adrenal cortical insufficiency is not a factor in the pathogenesis of bronchial asthma. The similarity in responsiveness of all groups to exogenous ACTH stimulation tended to rule out an adrenocortical insufficiency secondary to a depressed endogenous corticotropin production. Kelley *et al.*[9], noted that in patients with well established rheumatic fever there was an elevated circulating concentration of endogenous ACTH.

Davies[5] found that the 24-hour urinary 17-ketogenic steroid of severe asthmatic patients was within normal

TABLE 2.—BASELINE URINARY CORTICOSTEROID EXCRETION RATES PRIOR TO ACTH STIMULATION

Statistical Analysis No.	*Group Means Compared*	*Probability Value**
1.	C : NS†	.3>P>.2
2.	C : PS	.2>P>.1
3.	C : SO	.8>P>.7
4.	C : B	.8>P>.7
5.	NS : PS	.1>P>.05
6.	NS : SO	.8>P>.7
7.	NS : B	.6>P>.5
8.	PS : SO	.5>P>.4
9.	PS : B	.3>P>.2
10.	SO : B	1.0>P>.9

*Probability values >.05

†(C) Controls.
(NS) Asthmatics who had never received steroid therapy.
(PS) Asthmatics who had not taken corticosteroids for at least 2 weeks.
(SO) Asthmatics receiving corticosteroids at time of study.
(B) Asthmatics who had received both corticosteroids and intermittent corticotropin therapy prior to study.

TABLE 3.—ACTUAL INCREASE IN THE URINARY CORTICOSTEROID EXCRETION RATES AFTER EXOGENOUS ACTH STIMULATION

Statistical Analysis No.	*Group Means Compared*	*Probability Value**
1.	C : NS†	.4>P>.3
2.	C : PS	.5>P>.4
3.	C : SO	.4>P>.3
4.	C : B	.6>P>.5
5.	NS : PS	1.0>P>.9
6.	NS : SO	1.0>P>.9
7.	NS : B	.2>P>.1
8.	PS : SO	1.0>P>.9
9.	PS : B	.3>P>.2
10.	SO : B	.2>P>.1

*Probability values >.05

†(C) Controls.
(NS) Asthmatics who had never received steroid therapy.
(PS) Asthmatics who had not taken corticosteroids for at least 2 weeks.
(SO) Asthmatics receiving corticosteroids at time of study.
(B) Asthmatics who had received both corticosteroids and intermittent corticotropin therapy prior to study.

limits. He concluded that there was no relationship between the severity of the symptoms and the 17-ketogenic steroid excretion.

Ward *et al.*[24], Fischer[6], and Seely *et al.*[18] came to similar conclusions when they examined the corticosteroid blood levels of a group of patients suffering from rheumatoid arthritis and other rheumatic diseases.

If there is no relative adrenal cortical insufficiency, why are certain asthmatic patients benefited by cortisone and its analogues in amounts which do not seem to exceed the expected output of the patient's own adrenals? As yet, the need for steroid therapy cannot be related to any of the following: 1) A diminished endogenous corticotropin production (Reddy, Jenkins and Thorn[15]). 2) The possibility that inflamed tissues may need more steroids than their normal counterpart (Nelson and Samuels *et al.*[13]). 3) An imbalance in the pituitary-adrenocortical secretion, that is, mineralo-corticoid (STH) as opposed to the gluco-corticoid (ACTH) (Selye[19], Rosenberg, Woodbury and Sayers[16], Bauer[2], Sayers[17], and Hench[7]).

Equally unrewarding is the consideration that the responsiveness of the adrenal gland could have been limited by the persistent use of catechol amines (Tyler, Migeon and Castle[23]) or the presence of hypoxia secondary to transient or chronic airway obstruction (Barach and Bickerman[1]).

The recent observation that corticosteroids are bound by a protein grouping called transcortin (Slaunwhite and Sandberg[21]) suggests that the circulating corticosteroid deficiency might not be related to the total corticosteroid but only to the biologically active moiety present. It is conceivable that additional small amounts of exogenous or endogenous corticosteroids might saturate the binding system and so provide adequate biologically active corticosteroid levels.

Unfortunately, present measurements of the blood and urinary levels reflect only the total corticoids present. Further clarification of the status of the adrenal gland in the asthmatic patient may follow the use of techniques which determine not only the total circulating corticosteroids but also the biologically active moiety in particular.

Summary. Since 1955, 52 adult asthmatic and 19 control patients with inactive pulmonary tuberculosis have been studied to determine the capacity of their adrenal glands to respond to corticotropin.

Using the *t* test for comparing unpaired data, we found no statistically valid difference between the controls on the one hand and the asthmatic individuals on the other. This statement applied to all groups equally well regardless of whether they had received corticosteroids up to the time of the experiment, had taken none for at least 2 weeks, had taken both ACTH and corticosteroids, or were experiencing their first treatment with these hormones.

In view of these results, it is probable that adrenal cortical insufficiency was not a factor in the development of bronchial asthma on the patient population studied.

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SUMMARIO IN INTERLINGUA

Le Stato del Glandula Adrenal in le Patiente Asthmatic

Depost 1955, 52 adulte patientes asthmatic e 19 patientes de controlo (con inactive tuberculosis pulmonar) esseva studiate pro determinar le capacitate de lor glandulas adrenal a responder a corticotropina.

Per usar le test *t* pro comparar non-appareate datos nos trovava nulle statisticamente significative differentia inter le gruppo de controlo e le gruppo de individuos asthmatic. Iste constatation esseva equalmente applicabile a omne gruppos sin reguardo a si illes habeva recipite corticosteroides usque al tempore del experimento, si illes habeva prendite nulle durante al minus 2 septimanas, si illes habeva prendite ACTH e etiam corticosteroides, o si illes habeva lor prime experientia con iste therapias hormonal.

In vista de iste resultatos, il es probabile que insufficientia adreno-cortical non esseva un factor in le disveloppamento de asthma bronchial in le population de patientes studiate.

THE RELATIONSHIP OF FOOD INTAKE TO THE ABSORPTION OF POTASSIUM ALPHA-PHENOXYETHYL PENICILLIN* AND POTASSIUM PHENOXYMETHYL PENICILLIN† FROM THE GASTROINTESTINAL TRACT

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The absorption of various penicillins from the gastrointestinal tract is controlled by many variables. The chemical and physical characteristics of the specific penicillins, as well as the individual biological differences at any one time, affect the absorption pattern. Berlin and Brante[1] and Peck and Griffith[2] studied the effect of food upon the absorption of potassium phenoxymethyl penicillin. They were able to demonstrate substantially decreased penicillin serum levels when the antibiotic was administered with food.

The potential importance of antibiotic blood-level variations in the evaluation of research ventures and in the practical treatment of infections led to experiments with a new synthetic antibiotic, potassium alpha-phenoxyethyl penicillin, which were designed to study the effect of food intake upon the antibiotic serum levels.

Methods and Materials. Healthy adults of both sexes between the ages of 20 and 60 were used in this study. The antibiotic was in tablet form and contained 268 mg. of potassium alpha-phenoxyethyl penicillin from the same production lot.‡ The first set of experiments utilized 6 groups, each composed of 10 volunteers. Lunch served at 12:00 noon consisted of one cup of soup, one meat sandwich with butter and mayonnaise, and one glass of milk. One tablet of the antibiotic was administered as follows: Group I, 1 hour a.c.; Group II, 30 minutes a.c.; Group III, 15 minutes a.c.; Group IV, with meal; Group V, 1 hour p.c.; and Group VI, 2 hours p.c. Blood samples for penicillin assay were withdrawn at ½, 1, and 2 hours.

In the second experiment, 90 volunteers were randomized and given either 268 mg.

*Potassium alpha-phenoxyethyl penicillin: generic name is Potassium Penicillin 152; Bristol Laboratories' trade name is Syncillin. Bristol Laboratories' trade name for Syncillin abroad is Bendralan.

†Potassium phenoxymethyl penicillin: Penicillin V.

‡268 mg. of potassium alpha-phenoxyethyl penicillin and 250 mg. of potassium phenoxymethyl penicillin are molecular equivalents.

TABLE 1.—AVERAGE BLOOD LEVELS OBTAINED WITH POTASSIUM ALPHA-PHENOXYETHYL PENICILLIN

	No. of Subj.	*Ave. Age*	*Age Range*	*Ave. Weight*	*Weight Range*	*Sex*		½ *Hr.*	*Range*	*1 Hr.*	*Range*	*2 Hr.*	*Range*
						F	*M*						
1 Hour a.c.	10	36.5	21–56	150.1	110–215	6	4	3.5	1.4–5.8	3.3	1.8–4.6	0.9	0.5–1.3
½ Hour a.c.	9	23.3	20–43	143.5	126–170	3	6	2.76	0.6–5.5	2.5	1.0–3.8	0.52	0.3–1.0
¼ Hour a.c.	10	29.2	20–58	165	134–190	2	8	2.79	0.8–4.7	1.89	1.3–2.9	0.54	0.3–0.8
With meal	9	36.2	22–60	126.8	100–170	7	2	1.99	0.7–3.9	1.58	0.6–2.6	1.09	0.5–1.9
1 Hour p.c.	10	31.7	21–50	164.1	104–190	3	7	0.9	0.5–2.4	1.5	0.7–3.4	1.0	0.4–1.8
2 Hours p.c.	10	46.3	20–57	137.6	104–180	7	3	1.59	0.2–6.2	1.85	0.7–4.4	1.17	0.5–2.0

NOTE: All figures pertaining to blood levels are in micrograms per milliliter.

of potassium alpha-phenoxyethyl penicillin or 250 mg. of potassium phenoxymethyl penicillin at one of the following times: 1 hour a.c., with meal, 1 hour p.c., 2 hours p.c., or 3 hours p.c. The meal served at 12:00 noon was identical to that above. At 7:30 a.m. on the experiment day, all subjects ingested a breakfast which consisted of fruit juice, two eggs and milk. Blood samples for penicillin assay were withdrawn at 0, ½, 1, and 2 hours. Penicillin assays were performed by the cup plate method using *Sarcina lutea*, F.D.A. 1001, as the test organism. The assay procedure has a reproducibility of plus or minus 10%.

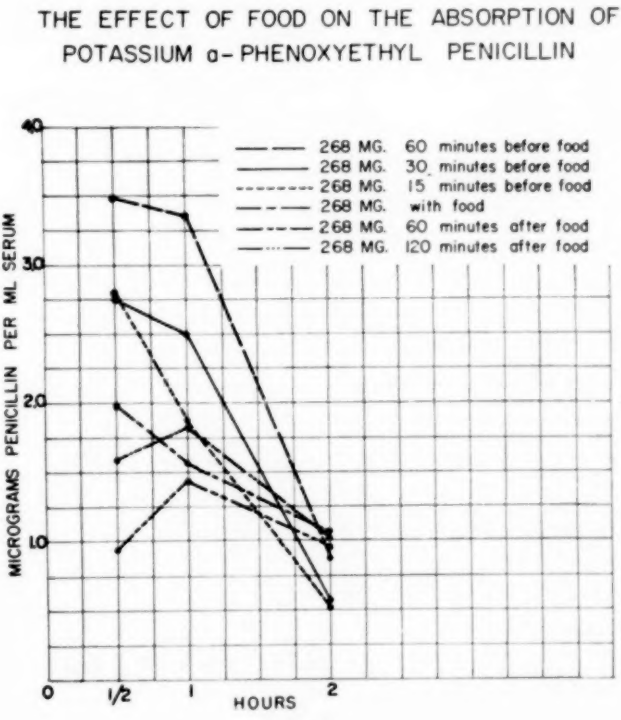

Fig. 1

Results. The results of the first set of experiments are presented in Table 1 and Fig. 1. The average penicillin serum concentrations obtained when potassium apha-phenoxyethyl penicillin was given before the test meal were considerably higher in the ½ and 1-hour samples than the concentrations obtained in similar blood samples when the test antibiotic was given after meals. The penicillin concentrations in blood samples taken 2 hours after antibiotic administration had minor variations between experiments, but they were essentially the same in the 6 experiments. The net results are peaked antibiotic serum curves in the *ante cibum* absorption studies and relatively flat curves in the *post cibum* absorption studies.

The results of the second experiment are presented in Table 2 and Fig. 2. These data demonstrate the same relationship between the time of antibiotic administration, with regard to meals, and the resulting penicillin serum concentrations. In each of the

TABLE 2.—AVERAGE BLOOD LEVELS OBTAINED WITH POTASSIUM PENICILLIN 152 AND PENICILLIN V

	Penicillin	*No. of Subjects*	*Ave. Age*	*Age Range*	*Ave. Weight*	*Weight Range*	*Sex*	
							F	*M*
1 Hour a.c.	152	9	36.7	21–56	151.8	118–205	3	6
	V	9	28.2	21–53	147.8	125–185	4	5
With meal	152	9	36	21–57	158	114–225	5	4
	V	9	32.1	22–47	146	100–212	6	3
1 Hour p.c.	152	9	33.7	21–52	158.7	115–182	4	5
	V	9	37	21–58	155.7	110–185	4	5
2 Hours p.c.	152	9	24	21–33	159.1	140–177	1	8
	V	9	24.2	21–50	163.1	140–190	1	8
3 Hours p.c.	152	9	28.6	21–54	154.3	125–205	3	6
	V	9	24.1	21–28	183.3	150–240	1	8

TABLE 2.—AVERAGE BLOOD LEVELS OBTAINED WITH POTASSIUM PENICILLIN 152 AND PENICILLIN V

	Penicillin	*0 Hour*	*½ Hour*	*Range*	*1 Hour*	*Range*	*2 Hours*	*Range*
1 Hour a.c.	152	0	2.78 NS	0.3–4.8	3.77 NS	0.3–9.8	1.12 *	0.6–2.3
	V	0	2.06	0.2–3.6	1.75	0.2–4.1	0.64	0.2–1.2
With meal	152	0	2.28 NS	1.0–5.3	1.66 NS	0.8–2.2	0.56 NS	0.4–0.8
	V	0	1.35	0.3–3.0	1.43	0.7–2.6	0.57 NS	0.2–0.9
1 Hour p.c.	152	0	0.96 NS	0.3–1.6	1.61 †	0.8–2.5	1.28 *	0.6–2.1
	V	0	0.47	0.1–1.7	0.66	0.2–1.3	0.53	0.2–1.0
2 Hours p.c.	152	0	1.41 NS	0.3–3.4	1.66 *	0.7–3.5	0.83 *	0.4–1.4
	V	0	0.64	0.1–2.6	0.80	0.4–1.1	0.52	0.2–0.8
3 Hours p.c.	152	0	1.27 †	0.5–1.7	2.22 ‡	1.4–4.3	1.11 *	0.4–1.9
	V	0	0.31	0.1–0.6	0.45	0.2–1.1	0.64	0.2–1.3

T test: NS No significant difference
* P = .05
† P = .01
‡ P = .001

NOTE: All figures are in micrograms per milliliter

individual experiments, the penicillin serum levels were substantially higher following the administration of phenoxyethyl penicillin than those following phenoxymethyl penicillin. With both penicillins, the presence of food in the gastrointestinal tract (ingested 0 to 3 hours before antibiotic administration) altered the pattern of the absorption curves. In the latter experiments, the curves portraying the concentration of penicillin in the serum were flat, as observed in the first group of studies.

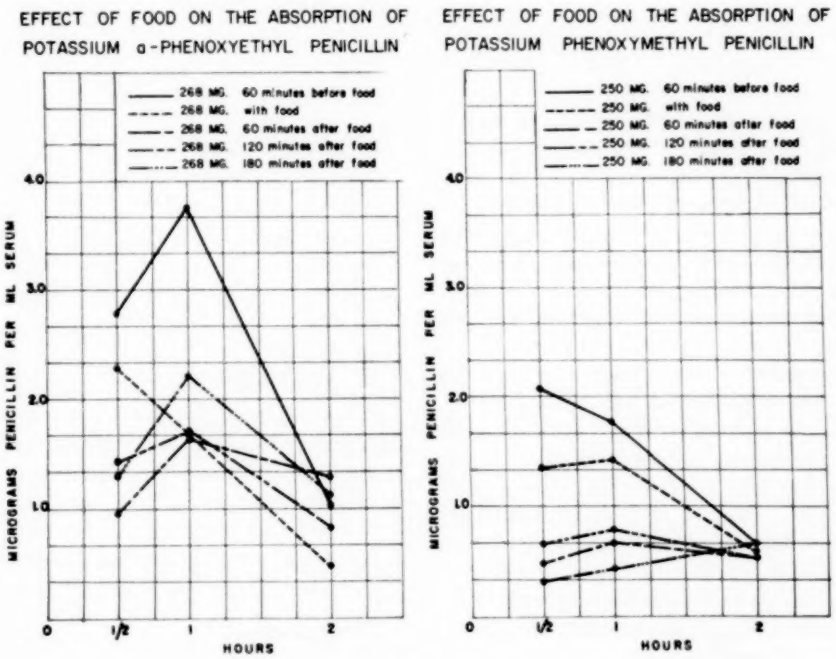

Fig. 2

T tests on the data obtained from the second experiment were performed to determine the significance of the differences in average antibiotic serum concentrations observed in this study. The results of this analysis are presented in Table 2. While considerable differences existed in average antibiotic serum concentrations obtained with the two test antibiotics, 7 of 15 differences were not statistically significant. Of the 8 observations where the differences between the serum levels were significant, 7 occurred in experiments in which food was ingested before the antibiotic administration.

Discussion. In 1959, Pindell and coworkers[3] reported their studies on the pharmacology of potassium alpha-phenoxyethyl penicillin. Using dogs as test animals, they were able to demonstrate, in artificially segmented gastrointestinal tracts, that potassium alpha-phenoxyethyl penicillin was absorbed best from the ileum, followed by the duodenum, stomach, and colon. The absorption curves from the dog's stomach and colon were relatively flat.

There is considerable similarity be-

tween the human absorption curves observed in this study and those observed by Pindell's group. The fasting patterns in humans suggest a combination of the duodenum-ileum absorption as observed in dogs. The nonfasting human patterns were similar to the dog stomach absorption curves. The apparent similarity of these observations in human and dog experiments would lead to the speculation that food in the gastrointestinal tract prior to antibiotic administration acts as a mechanical blocking agent to the passage of the antibiotic to the high absorption areas of the ileum and duodenum.

Most of the penicillin-sensitive organisms such as Group A Streptococcus, gonococcus, pneumococcus, and others, are inhibited *in vitro* by antibiotic concentrations considerably less than 1.0 μg. per ml. Both potassium alpha-phenoxyethyl penicillin and potassium phenoxymethyl penicillin are known to be effective agents in treating infections caused by the above microorganisms. Under the various conditions of this study, the lowest antibiotic serum concentration obtained with either penicillin was in excess of the minimum inhibitory concentration necessary for most susceptible organisms; theoretically, it would be clinically effective. Therefore, are there any clinical advantages associated with the increased penicillinemia observed following the oral administration of potassium alpha-phenoxyethyl penicillin over that observed with potassium phenoxymethyl penicillin? Probably not, but the scientific answer to this question is unknown.

Summary and Conclusions. 1. Potassium alpha-phenoxyethyl penicillin (268 mg.) was administered orally to groups of human volunteers at 60, 30, and 15 minutes *ante cibum, cum cibum,* and 60 and 120 minutes *post cibum.* The average penicillin concentrations so achieved at ½ hour were: 3.5, 2.76, 2.79, 1.99, 0.9, and 1.59 μg. per ml. respectively; at 1 hour they were: 3.3, 2.5, 1.89, 1.58, 1.5, and 1.85 μg. per ml. respectively; at 2 hours they were: 0.9, 0.52, 0.54, 1.09, 1.0, and 1.17 μg. per ml., respectively.

2. In a comparison study, 268 mg. of potassium alpha-phenoxyethyl penicillin or 250 mg. of potassium phenoxymethyl penicillin were administered orally to groups of human volunteers at 60 minutes *ante cibum, cum cibum,* and 60, 120, and 180 minutes *post cibum.* Following the administration of potassium alpha-phenoxyethyl penicillin, the average penicillin serum concentrations at ½ hour were: 2.78, 2.28, 0.96, 1.41, and 1.27 μg. per ml. respectively; at 1 hour they were: 3.77, 1.66, 1.61, 1.66, and 2.22 μg. per ml. respectively; at 2 hours they were: 1.12, 0.56, 1.28, 0.83, and 1.11 μg. per ml. respectively. Following the administration of potassium phenoxymethyl penicillin, the average penicillin serum concentrations at ½ hour were: 2.06, 1.35, 0.47, 0.64, and 0.31 μg. per ml. respectively; at 1 hour they were: 1.75, 1.43, 0.66, 0.80, and 0.45 μg. per ml. respectively; at 2 hours they were: 0.64, 0.57, 0.53, 0.52, and 0.64 μg. per ml., respectively.

3. It would appear that orally administered potassium alpha-phenoxyethyl penicillin is absorbed better from the gastrointestinal tract than potassium phenoxymethyl penicillin whether the subject is fasting or has ingested food before, with, or after the antibiotic.

4. The described experiments suggest that to obtain maximum penicillin serum concentrations, potassium alpha-phenoxyethyl penicillin and potassium phenoxymethyl penicillin should be administered before meals.

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SUMMARIO IN INTERLINGUA

Le Relation Inter le Consumo de Alimento e le Absorption, ab le Tracto Gastrointestinal, de (1) Penicillina Alpha-Phenoxyethylic a Kalium e (2) Penicillina Phenoxymethylic a Kalium

1. Penicillina alpha-phenoxyethylic a kalium (268 mg) esseva administrate per via oral a gruppos de voluntarios human 60, 30, e 15 minutas ante cibo, con cibo, e 60 e 120 minutas post cibo. Le resultante concentrationes medie de penicillina in le sero esseva post ½ hora: 3,5, 2,76, 2,79, 1,99, 0,9, e 1,59 μg per ml, respectivemente; post 1 hora: 3,3, 2,5, 1,89, 1,58, 1,5, e 1,85, e post 2 horas: 0,9, 0,52, 0,54, 1,09, 1,0, e 1,17.

2. In un studio de comparation 268 mg de penicillina alpha-phenoxyethylic a kalium o 250 mg de penicillina phenoxymethylic a kalium esseva administrate per via oral a gruppos de voluntarios human 60 minutas ante cibo, con cibo, e 60, 120, e 180 minutas post cibo. Post le administration de penicillina alpha-phenoxyethylic a kalium le concentrationes medie de penicillina in le sero esseva post ½ hora: 2,78, 2,28, 0,96, 1,41, e 1,27 μg per ml, respectivemente; post 1 hora: 3,77, 1,66, 1,61, 1,66, e 2,22; e post 2 horas: 1,12, 0,56, 1,28, 0,83, e 1,11. Post le administration de penicillina phenoxymethylic a kalium le concentrationes medie de penicillina in le sero esseva post ½ hora: 2,06, 1,35, 0,47, 0,64, e 0,31, μg per ml, respectivemente; post 1 hora: 1,75, 1,43, 0,66, 0,88, e 0,45; e post 2 horas: 0,64, 0,57, 0,53, 0,52, e 0,64.

3. Apparentemente penicillina alpha-phenoxyethylic a kalium es absorbite melio ab le tracto gastrointestinal que penicillina phenoxymethylic a kalium sin reguardo a si le subjecto es jejunante o ha ingerite alimento ante, con, o post le antibiotico.

4. Le experimentos describite indica que le maxime concentrationes de penicillina in le sero es obtenite quando penicillina alpha-phenoxyethylic a kalium o penicillina phenoxymethylic a kalium es administrate ante cibo.

PITFALLS IN THE DIAGNOSIS AND TREATMENT OF PERNICIOUS ANEMIA

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Pernicious anemia, a megaloblastic maturation arrest of erythropoiesis often with associated neurologic changes in the posterolateral tracts of the spinal cord and with gastric achlorhydria, results from inadequate absorption of orally ingested cyanocobalamine (vitamin B_{12}). A glycoprotein-like factor(s) secreted by normal gastric mucosa permits absorption of vitamin B_{12} in pernicious anemia patients. This substance, named intrinsic factor, was described by Castle as a substance which when given with extrinsic factor (vitamin B_{12}) by mouth will produce a therapeutic response in pernicious anemia in relapse (Bethell *et al.*[3], Castle[4], Castle and Ham[5]). Investigators have found that vitamin B_{12} absorption may be slightly modified by or related to pregnancy, age, hypothyroidism, steroid administration, gastrectomy and pyridoxine deficiency (Chow *et al.*[7]). Furthermore, divided dosage, size of dose, and per cent saturation of intrinsic factor with vitamin B_{12} (Skouby and Kristensen[15]) have been postulated as important in the effectiveness of various oral preparations of vitamin B_{12} used in the treatment of pernicious anemia. Currently, a sugar, d-sorbitol, combined with vitamin B_{12} has been reported to enhance oral absorption (Greenberg *et al.*[9]). Some studies regarding the effectiveness of this combination have been performed and will also be reported herein.

It is often difficult to separate pernicious anemia with associated combined posterolateral sclerosis or degeneration of the spinal cord from peripheral neuropathy secondary to alcoholism, tabes dorsalis, or age alone. The hematologic picture may remain normal because of the oral administration of small amounts of folic acid. One needs only to glance at a current drug listing to appreciate the numerous commercially available multivitamin and hematinic preparations, especially those for geriatric use, which contain folic acid. Case 1 illustrates this problem.

Once diagnosed, maintenance treatment of pernicious anemia with intramuscular crystalline vitamin B_{12}, 30 μg. every 2 weeks, has proven satisfactory (Lear and Castle[10]). Oral preparations containing vitamin B_{12} and stomach liver concentrate combinations are also available. The source of intrinsic factor in all these preparations is from animals. The long-term value of oral medication for pernicious anemia is difficult to evaluate because

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TABLE 1.

		Vit. B_{12} Alone			*B_{12} + Sorbitol*			*B_{12} + Intrinsic Factor*			*B_{12} + Intrinsic Factor + Sorbitol*		
		Urine			*Urine*			*Urine*			*Urine*		
Patient	*Diagnosis*	*Vol.*	*Sp. Gr.*	*% $B_{12}Co^{60}$†*	*Vol.*	*Sp. Gr.*	*% $B_{12}Co^{60}$*	*Vol.*	*Sp. Gr.*	*% $B_{12}Co^{60}$*	*Vol.*	*Sp. Gr.*	*% $B_{12}Co^{60}$*
1. J.V.	Normal	900	1.025	28	1000	——	30	1000	1.018	12	900	1.020	27
2. R.P.	Normal	800	1.027	7	1200	1.015	8						
	24–48 hr. urine	1400	1.016	1.5	1800	1.016	2						
3. D.V.	Gastric achlorhydria	2200	1.010	12	1600	1.011	8	1500	1.010	20	1800	1.012	12
4. F.W.	Post subtotal gastrectomy	1500	1.013	3	1000	1.020	9	1200	1.016	12*	800	1.017	19*
	24–48 hr. urine	1500	1.012	0	800	1.026	0	1000	1.020	0	1000	1.015	0.6
5. J.H.	Pernicious anemia	1300	1.030	0.2	1700	1.020	0.2	1800	1.010	13*	1800	1.021	8*
	24–48 hr. urine	700	1.032	0.7	1700	1.020	0						
6. F.M.	Pernicious anemia	600	1.025	0.6	1100	1.018	0.5	1000	1.021	8*			
	24–48 hr. urine	800	1.025	0.2	1200	1.020	0	1250	1.021	3*			
7. C.C.	Pernicious anemia	1500	1.016	3	950	1.018	3	750	1.023	8*	840	1.019	5*
8. H.C.	Pernicious anemia	2300	1.009	1.7	2500	1.010	0.9	2400	1.025	16*	2500	1.009	15*
	24–48 hr. urine	2100	1.009	0.5	2350	1.006	1.3				3300	1.007	4
9. J.H.	Pernicious anemia	1300	1.013	1.3	800	1.021	3.5	1200	1.015	15*	600	1.021	17*

*Pooled normal human gastric juice used in place of commercially prepared intrinsic factor.
†% of orally administered $B_{12}Co^{60}$ in 24- or 48-hour urine determined by Schilling technique.
‡Sorbitol given as 1.0 gm. of D-Sorbitol (Micropulverized RM 4121 ISO#69392).

vitamin B_{12} stored in the liver has a biologic half-life of one year (Schloesser and Schilling[13]). Remissions without treatment may last for several years. Case 2 illustrates the development of resistance to an orally administered intrinsic factor preparation.

Materials and Methods. The diagnosis of pernicious anemia was established in reported patients by examination of peripheral blood and bone marrow, determination of histamine-fast gastric achlorhydria, and by the Schilling test[11,12] for absorption of radioactive-cyanocobalamine (Cobalt^{60} vitamin B_{12} or $B_{12}Co^{60}$) both before and after addition of a potent intrinsic factor preparation. Less than 3% absorption of orally administered $B_{12}Co^{60}$ as measured in 24-hour urine excretion was considered diagnostic of pernicious anemia in absence of gastrectomy if normal absorption was demonstrated by addition of intrinsic factor to the $B_{12}Co^{60}$. The test was performed using 0.5 mg. $B_{12}Co^{60}$ containing 0.5 microcuries radioactivity (Table 2). The majority of tests (Table 1) were performed using the same amount of radioactive vitamin but raising total oral vitamin B_{12} content to 1.0 mg. using carrier or "cold" vitamin B_{12}. The oral dose was given fasting and followed by an intramuscular dose of 1000 mg. of "cold" vitamin B_{12}, and the urine collected for 24 hours. When a 24- to 48-hour urine was collected a second intramuscular dose of 1000 mg. B_{12} was given at the beginning of the second period, but no further oral radioactive vitamin.

Where commercially prepared intrinsic factor was unsatisfactory, pooled filtered, neutralized (some lyophilized) human gastric juice was used. In 5 patients with proven pernicious anemia and in 4 patients without pernicious anemia, one with gastric achlorhydria and one with subtotal gastrectomy, the effect of the addition of sorbitol to $B_{12}Co^{60}$ with and without intrinsic factor on absorption of the $B_{12}Co^{60}$ was determined and recorded in Table 1. Sorbitol is a white crystalline solid, soluble in water, sweet, naturally occurring in fruits, and is rapidly absorbed like other sugars. Our supply was kindly furnished by the Smith, Kline and French Company, Philadelphia, Pa.

TABLE 2.—RESULTS OF VITAMIN $B_{12}Co^{60}$ ABSORPTION TESTS IN A PERNICIOUS ANEMIA PATIENT WHO HAD BECOME REFRACTORY TO INTRINSIC FACTOR OF HOG SOURCE

Date	*Test*	*Urine*	*% of Orally Administered $B_{12}Co^{60}$ in 24-hour Urine*
7/28/59	0.5 microcuries $B_{12}Co^{60}$ as 0.5 μg. B_{12} in H_2O	730 ml.	0.7%
8/1/59	Same plus capsule commercial hog intrinsic factor equivalent to activity of 25 to 50 ml. gastric juice.	600 ml.	0.9%
8/8/59	Normal whole human gastric juice —50 ml. frozen 18 mos.	630 ml.	6.5%
8/19/59	Fresh normal human gastric juice —filtered, neutralized, and dialyzed—50 ml. equivalent	1000 ml.	16.5%

Results. A. CASE 1. W.C.S., a 51-year-old white maintenance foreman, was hospitalized because of burning of the soles of both feet, history of tingling in the fingertips for 2½ months, and progressive paresthesias of his feet and lower legs. Physical examination revealed a positive Romberg test, peripheral blunting to pinprick, absent vibratory sense in both legs, and absent knee and ankle deep tendon reflexes. Laboratory tests revealed hemoglobin 15.1 gm.%, hematocrit 46%, leukocytes 6250 per c.mm., BUN 10 mg. per 100 ml., platelets adequate, and BSP dye retention 2% at 45 minutes. No free gastric acid was noted after histamine stimulation. Pernicious anemia was not considered because of the normal blood values. Spinal fluid examination was normal. The patient was maintained on a daily multiple vitamin preparation containing 2.5 mg. folic acid and 5 mg. of crystalline vitamin B_{12}.

He was rehospitalized one month later

because of continued difficulty in walking and loss of urinary bladder control. The patient was now unable to walk alone or drive his car. Vibratory sense was absent to the sternum, abdominal reflexes were absent, and bilateral Babinski signs were present. Blood values were again normal. Excretion of vitamin $B_{12}Co^{60}$ by the Schilling test was 0.35% in an adequate 24-hour urine specimen. With addition of a capsule of commercial hog intrinsic factor to the $B_{12}Co^{60}$, 24-hour excretion was 11%. The patient was placed on parenteral vitamin B_{12} with marked improvement and almost complete reversal of the neurologic changes.

The initial failure to make a correct diagnosis in this patient was caused by lack of recognition that the multivitamin preparation taken by this patient contained enough folic acid to block the development of a typical hematologic picture of pernicious anemia.

B. CASE 2. L.D., a 70-year-old white woman, was hospitalized in July, 1959, with symptoms of marked anemia. Past medical history revealed that in August, 1945, she was first hospitalized with the chief complaint of hypersensitivity reaction to parenteral liver injections. At that time there had been a 5-year history of intermittent weakness, sore tongue, numbness of feet, clumsiness, paresthesias, inability to walk at night. She had been treated with intermittent oral and later parenteral liver preparations. Admission in 1945 for desensitization to parenteral liver. Physical examination then revealed blood pressure 210/125 mm. Hg, absent knee and ankle reflexes, and decreased vibratory sense at the ankles. The hemoglobin was 14.1 gm.%, hematocrit 45%, and gastric analysis revealed histamine-fast achlorhydria. Desensitization was not carried out and treatment consisted of 12 capsules daily of an oral liver-stomach concentrate. This was changed later to a capsule of folic acid 2 mg., intrinsic factor 1 USP unit, and 15 μg. of vitamin B_{12}. Oral therapy was continued until April, 1948, when symptoms of anemia recurred. The red cell count was 1.4 million per c.mm., the hemoglobin 4.1 gm.%, and the leukocytes numbered 3100 per c.mm. There were 25 nucleated erythrocytes per 100 white cells, and platelets were decreased. Bone marrow aspiration revealed findings consistent with pernicious anemia. She was treated with folic acid and Ventriculin 20 gm. per day and was not seen again until the current admission. During this 11-year interim she continued on an oral iron-liver-stomach liquid hematinic. Physical examination on this admission was similar to that of 1945.

Laboratory studies revealed a hemoglobin of 4.5 gm.%, mild leukopenia and thrombocytopenia. The patient was treated with parenteral vitamin B_{12} and responded promptly. Two weeks later the hemoglobin was 9.7 gm.% and one month after onset of therapy 11.9 gm.%. The Schilling test results are shown in Table 2.

The results of these tests demonstrate failure to absorb vitamin B_{12} with hog intrinsic factor but retained ability to absorb vitamin B_{12} with fresh active human gastric juice.

C. Sorbitol has been claimed to increase absorption of vitamin B_{12} in normal patients (Chow, Horonick and Okuda[6]), although not significantly in pernicious anemia patients (Ellenbogen, Herbert and Williams[8]). Our studies of this material in a normal patient with gastric achlorhydria and in patients with free gastric acid show no significant increase in vitamin B_{12} absorption with or without added intrinsic factor. The absorption and urinary excretion test of $B_{12}Co^{60}$ (Schilling) has been used for measuring purposes in these and an additional 5 patients with proven pernicious anemia (Table 1). The normal variation in the absorption of vitamin B_{12} can be appreciated by these results. It would seem, therefore, that interpretation of small variations to indicate increased or decreased absorption may be invalid. One would certainly expect that a substance which enhanced vitamin B_{12} absorption would be most evident in the pernicious anemia subject given vitamin B_{12} plus intrinsic factor.

Discussion. Intrinsic factor, an unknown substance or combination of several substances found in gastric juice, combines with vitamin B_{12} to increase its absorption. Oral prepara-

tions for the treatment of pernicious anemia are prepared from animal pyloric mucosa or whole stomach and are standardized by their activity in patients with pernicious anemia in relapse. Loss of effectiveness after long continued therapy through an unknown blockade mechanism or immunologic resistance is now being recognized (Berlin *et al.*[1], Bethell *et al.*[2], Schwartz, Lous and Meulengracht[14]). It appears that some individuals with pernicious anemia can become refractory to animal intrinsic factor. In view of the large number of available oral compounds which contain intrinsic factor and vitamin B_{12}, the physician must remain continually alert to this potential hazard. The treatment of pernicious anemia with parenteral vitamin B_{12} is the treatment of choice. It is of interest that in Case 2 the patient had developed a prior hypersensitivity reaction to crude liver injection and subsequently became refractory to the intrinsic factor of animal source. Lest the clinician be misled, additive substances in multiple vitamin compounds do not appear to enhance vitamin B_{12} absorption and should not be relied upon in conditions of vitamin B_{12} deficiency. Because of the many available multivitamin preparations containing folic acid, one must be alert to the early neurologic signs of pernicious anemia. Neurologic degeneration may be accelerated in a situation where folic acid is administered without vitamin B_{12} (Vilter, Vilter and Spies[16]). It is our belief that all patients with peripheral neuritis or paresthesias should have a determination for free gastric acid and, if achlorhydria is demonstrated, a vitamin $B_{12}Co^{60}$ absorption study (Schilling test) should be performed.

Summary. The addition of sorbitol to vitamin B_{12} preparations with or without intrinsic factor does not appear to increase its absorption in normal patients or those with pernicious anemia. The diagnosis of pernicious anemia has become complicated by the presence of numerous geriatric multivitamin preparations containing folic acid, vitamin B_{12}, and intrinsic factor concentrates. Oral preparations for the treatment of pernicious anemia or other vitamin B_{12} deficiency states may result in suboptimal treatment or eventual clinical relapse. The clinician must be alert to these pitfalls in diagnosis and treatment and must rely more on the use of determinations of histamine fast achlorhydria and radioactive vitamin B_{12} absorption tests than on the presence of macrocytic or megaloblastic anemia. The mainstay of the treatment of pernicious anemia remains parenteral vitamin B_{12} in adequate dosage for the rest of the patient's life.

Reprints from: Radioisotope Service, Veterans Administration Hospital, 2215 Fuller Rd., Ann Arbor, Michigan.

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SUMMARIO IN INTERLINGUA

Captiositates in le Diagnose e le Tractamento de Anemia Perniciose

Le addition de sorbitol a preparatos de vitamina B_{12} con o sin factor intrinsec non pare promover su absorption in patientes normal o in patientes con anemia perniciose. Le diagnose de anemia perniciose ha devenite plus complicate per le presentia de numerose preparatos multivitaminic geriatric que contine acido folic, vitamina B_{12}, e concentratos de factor intrinsec. Preparatos oral pro le tractamento de anemia perniciose o altere statos de carentia vitaminic de B_{12} pote resultar in un tractamento suboptimal o, in le curso del tempore, in recidiva clinic. Le clinico debe esser conscie del existentia de iste fontes de error diagnostic e therapeutic e debe fider se plus al uso de determinationes de histamino-resistente achlorhydria e tests de absorption de radioactive vitamina B_{12} que al presentia de anemia macrocytic o megaloblastic. Le elemento le plus importante in le tractamento de anemia perniciose remane vitamina B_{12} parenteral in doses adequate pro le duration del vita del patiente.

PROGRESS
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SURGERY

UNDER THE CHARGE OF

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URINARY DIVERSION

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BROADLY considered, the term urinary diversion indicates the changing of the normal course of urinary flow from the kidney to the body exterior by surgical alterations of its proper channels, or by conversion to others, surgically created for the purpose, or both. Technical procedures for its accomplishment may be limited and simple or extensive and complex. The simple limited techniques (for example, urethrotomy, cystotomy, cutaneous ureterostomy and nephrostomy), are in the main familiar because of early development and long usage. The more recently devised diversionary procedures are not, because to a large extent they are still in the category of surgical innovations, and concerning them there is less general knowledge and considerable speculation. As their usage increases, some of them will no doubt be discarded and others accepted and standardized according to particular indications.

It is the purpose of this writing to examine as comprehensively as possible, certain of the more promising of recently developed techniques for urinary diversion. This is done in the hope that such will prove of value to some in the management of disorders where the procedure may be essential to palliation for cure.

GENERAL CONSIDERATIONS. It may be generally stated that while the pro-

*Deceased.

cedures for urinary diversion have changed, the indications for its performance have not[14,34,37,63]. These indications may be largely included under a single indication with a few additional ones. This is actual or impending obstruction of urinary flow through its normal channels. Congenital anomalies, inflammation, metabolic disorders, and neoplasms may all produce obstruction of the various parts of the urinary tract[1]. These causes represent theoretically an almost limitless variety of etiological agents of urinary obstruction, all having the common feature of impeding or occluding urinary flow through the various components of the urinary tract. There are however, other indications for diversion, far less frequently encountered which are not obstructive in character. One of these is in conditions where diversion of urinary flow is advisable to create conditions optimal for healing of lesions incident to trauma or inflammation[1,14]. The other is for the relief of disorders in which severe pain is produced by urinary flow through the normal channels[14,47]. Thus, the principal indications for urinary diversion may be included under one, a consideration of any two, or all three of the following: 1) relief of impending or actual obstruction, 2) the promotion of healing, 3) the elimination of pain.

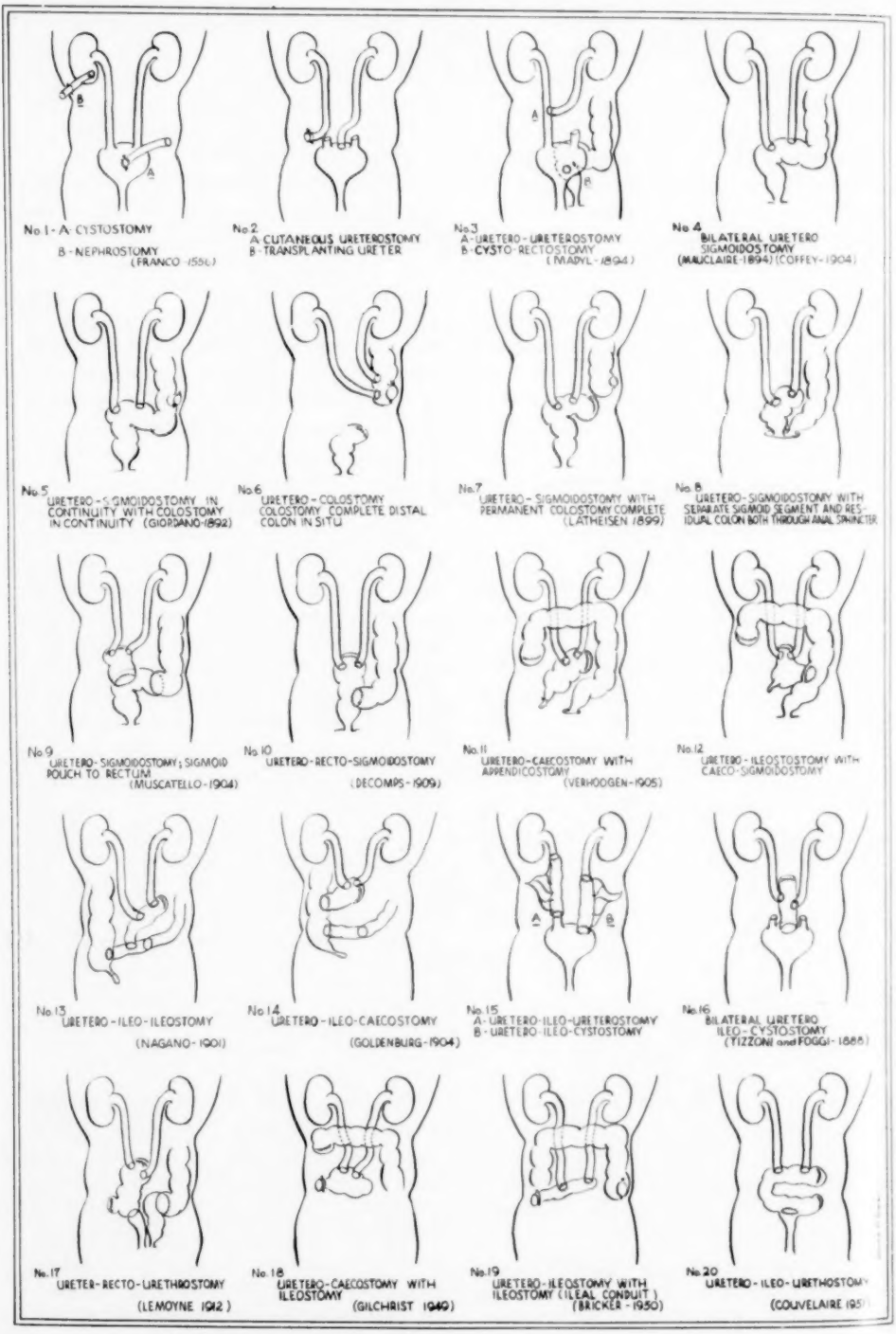
While it is true that the indications for the performance of urinary diversion have remained generally the same, the palliative and therapeutic possibilities have been greatly improved and expanded by lately developed diversionary techniques[6,24,28,35,49]. This is because their successful performance allows in many instances the complete removal of the permanently disabling portion of the urinary tract and adjacent lesions, whether obstructive, unhealing or painful. In short, by such diversionary procedures, satisfactory functional substitutions are made for diseased portions of involved urinary and other structures, allowing palliative or therapeutic excisions of an extent hitherto considered impossible[16,23,36].

As has been indicated above, all the significant recently evolved diversionary procedures have two common factors: 1) the (use) by anatomical interposition of some portion of the digestive tract to replace or substitute for the involved portion of the urinary channels; and 2) the anatomical and physiologic adaptation of the replacing or substituting gastrointestinal segment locally and generally to the function of a urinary repository or conduit.

Anatomical interposition of various segments of the gastrointestinal tract to form some portion of the urinary channel is the common feature of the recently developed urinary diversion procedures. The various procedures vary technically from each other only in a) the segment of the gastrointestinal tract (large or small bowel) employed and b) the portion of the urinary tract that has been replaced (See Fig. 1).

Thus, exclusive of the kidney itself, whose excretory function cannot be replaced or supplanted, all parts of the urinary tract have been substituted by using anastomotic connections to various segments of small or large bowel. The ureters, bladder and urethra, all or in part, have been subjected to diversionary replacement with bowel segments[21,26,42,51,56,64].

This has been technically possible because of the fact that selected segments of both the small and large bowel can be isolated, mobilized and transposed over considerable distance, with their blood supply sufficiently intact to maintain complete viability. Moreover, the natural lumen, peristalsis, and selective absorption properties



DIVERSIONARY PROCEDURES - FIGURE No.1 20 PANELS; No.1 Through No.20
CROWLEY, R.T. and SWIGART, L.L.

Fig. 1

of bowel segments (as will be noted later) in the main lend themselves to containing and advancing of urinary flow. Considering this, it is appropriate at this point to note that so far as actual operative procedure is concerned, use of small bowel segments for diversion has certain inherent advantages as compared with the employment of portions of the colon. These technical advantages of small bowel segments over those of the colon are apparent when the following comparative anatomical features are recalled:

1. The small bowel, due to the freedom of its mesenteric attachments, is more readily mobilized and interposed between various urinary or other structures[3,5].
2. The blood supply is considerably less precarious than that of the colon. The profuse collaterals of its mesenteric and intramural circulation are far more extensive than those of the colon, thus giving a greater assurance of viability in any isolated segments[3,5].
3. Peristalsis in the small bowel, due to its muscular and nervous patterns, is more active and continuous than in the colon, lending itself, at least theoretically, better to aiding the passage of contained urine[31,68].
4. The wall of the small bowel is thicker and its serosal covering more complete than those of the colon, allowing greater security of suture lines in the performance of actual anastomosis between the various portions of the urinary tract or other structures[3,5].
5. The bacterial flora of the small bowel is less liable to cause ascending urinary infections than that of the large[4].

These inherent advantages of the use of small bowel segments over those of the large are of considerable technical consequence, and as will be seen later, weigh heavily in the selection of particular procedures selected for indicated urinary diversion.

But more important than the anatomical considerations concerned in operative techniques are those of the ultimate function of the organ (large or small bowel segment) which has been successfully interposed to substitute for the disordered or excised portion of the urinary tract. As noted above, the most significant feature is in terms of function, and not in how readily the technical procedure is performed. Hence, the primary consideration in any diversionary procedure is the anatomical and physiologic adaptation of the substituting bowel segment (small bowel or colon) locally and generally to the function of the replaced urinary structure, whether repository or conduit.

This adaptation is then measured by the capacity of the interposed bowel segment to meet the following requisites:

1) Conduction of urinary flow without delay or obstruction.
2) Absence of absorption of urinary products from the interposed bowel segment into the general circulation.
3) Voluntary control of urinary flow.
4) Freedom from infection in the residual urinary tract.

Concerning the above, it is scarcely necessary to point out that the normal urinary tract performs these functions optimally, urine flows from the kidney to the exterior continuously. There is no absorption of waste products from the urinary tract into the blood stream. The expulsion of urinary volume to the exterior is more or less a willed procedure and, under ordinary circumstance, the tract is relatively free from

pathogenic organisms and therefore from infection.

The measure of adaptation, then, lies in how closely any diversionary procedure, however difficult its technical accomplishment, can more or less permanently fulfill these requisites. Obviously, no interposed foreign organ can completely supplant the ones naturally designed for a specific function. Evaluation of the various procedures contrived for urinary diversion is therefore a matter of how closely bowel segments (small or large) can simulate the normal urinary channels in: conducting or storage of urine, reducing undue absorption of deleterious urinary products, in allowing voluntary elimination to the body exterior (continence), and keeping infection of the residual urinary tract to a tolerable minimum.

Mention has already been made of the general superiority of the small bowel over the colon as a urinary conduit. It is appropriate to specify at this juncture that the most adaptable portion of the small bowel is probably the ileum in its terminal portions. This is because:

1) The disposition of its peritoneal attachments and blood supply allow the utmost freedom in transposition of segments of varying length between various portions of the urinary tract, the body exterior, or other hollow organs.
2) Its thick muscular walls and serosal covering lend themselves well to security of anastomosis to various portions of the urinary tract.
3) Its large lumen offers no obstruction to urinary flow of any volume.
4) Its inherent peristalsic properties ensure in the main a rapid evacuation of urinary volume.
5) In short segments, the terminal ileum is an area of low absorbability. That is to say, that the waste products which may be contained in the lumen of isolated segments, are not likely to be absorbed in significantly deleterious quantities into the general circulation[8].
6) Bacterial flora of the ileum contains less pathogenic organisms, reducing likelihood of ascending urinary infection.

Thus, in terms of adaptability, the ileum is the most useful portion of the small bowel as a substitute urinary conduit in almost any diversionary procedure.

This fact is emphasized by a comparison of the basic factors of adaptability (*vide supra*) with respect to the large bowel.

1. The mesenteric attachments and blood supply of the large bowel allow less freedom in the transposition of large bowel segments between various of the urinary or other tracts.
2. The thin muscular walls and incomplete serosal covering of the colon are likely to threaten the security of the essential anastomosis essential in establishing the diverted urinary flow.
3. The one advantage of the large bowel segment is in its relatively great diameter of lumen, allowing less possibility of obstruction, but
4. Peristalsis in the large bowel is less effective in the essential process of forwarding the progress of any urinary conduit. Therefore, urinary stasis is more likely to supervene.
5. Segment for segment, selective absorption of deleterious products of any urinary content is greater in the large bowel. Briefly stated, length of segment for length of segment, it may be said that more toxic products of any urinary con-

tent are more likely to be retained and therefore absorbed from any large bowel segment than from one of the terminal ileum[57].

6. The colon contains quantitatively and qualitatively more pathogenic organisms, thus increasing the hazard of ascending urinary infection[19,43].

Hence, it has currently come about that in the essential reckoning of diversionary procedures, the use of segments of the terminal ileum are preferred where possible to use of similar sections of the colon.

There are, however, possibly specific situations in which use of the terminal ileum segments may be difficult or impossible, where colonic segments may be substituted. This will be noted later[33,62].

So far, in the general technical and adaptive considerations cited above concerning diversionary procedures, little mention has been made concerning the feature of voluntary control of urinary flow of the diverted urinary tract to the body exterior. Having established the fact that various portions of the urinary system (excluding the kidney parenchyma proper) can be substituted anatomically and functionally, much ingenuity has been evidenced in attempting to attain voluntary control of urinary excretion. In brief, every effort has been made to perfect diversionary procedures which will allow urinary passage out of the body at will of the subject, or in a manner approximating the normal process. This objective has been more than a little overemphasized in both experimental and clinical reports. It also warrants close examination.

The voluntary excretion of urine under normal conditions ultimately depends upon one principal factor[4,40,52]. This is concerned with voluntary muscle or muscles which can be controlled at will. The normal voluntary act of micturition in the human, reduced to its simplest progression of events is: 1) the distension of the bladder with urine; 2) the consciousness of this disturbance; 3) the voluntary relaxation of the occluding bladder sphincter muscle with the simultaneous contraction of the bladder musculature, thus allowing and *propagating* expulsion of urine through the urethra to the body exterior.

The success of any procedure for urinary diversion designed to allow voluntary control rests upon the extent to which this normal emptying action can be simulated without sacrificing the other requisites of adaptation above named: unobstructed urinary flow, minimal absorption of deleterious urinary products, and minimal hazard of ascending infection of the essential remaining portion of the urinary tract.

Concerning this, several observations are in order. The number and extent of the various currently employed diversionary procedures, as will be further detailed later, is impressive. They vary from short length substitutions of bowel with little alteration in position to long bowel segments transposed into remarkably devious and remote anatomical situations[6,16]. Practically every possible anastomotic communication between the diversionary bowel segment (large or small) and the various portions of the urinary tract has been recorded experimentally or clinically (see Fig. 1). But regardless of the nature and extent of the procedure, so far as the single factor of preservation of voluntary passage of urine or continence is concerned, the degree of continence is determined by the degree to which the natural body sphincters, urinary or digestive, can be utilized. In brief, no reconstituted anatomical arrangement can even closely approximate a normally func-

tioning voluntary sphincter muscle. Considerable ingenuity has been expended in the innovation of diversionary procedures directed toward the preservation of the urinary sphincter action or to its substitution by that of the digestive tract (rectal). Suffice it to say, that preservation of either the genitourinary or the rectal sphincter action, or both, is often inadvisable or impossible. This is true because the sphincters of both systems may be either too diseased to function with any efficiency or must be eliminated by excision involved in the necessary surgery. Thus it is that diversionary procedures may be amended in two categories:

a) Those in which sphincteric action of either the normal genitourinary or substitute gastrointestinal tract (rectal) can be preserved or

b) those in which either or both sphincteric actions must be disregarded or sacrificed because of primary disease or necessary excisions.

Concerning the first category in which normal sphincteric action either of the urinary bladder iself or the substituting rectal sphincter may be retained, it may be said that such procedures are limited to less extensive disorders of the urinary channels: here relatively conservative surgical excisions essential in their palliation or cure are possible along with sphincter preservation. In these, interpositions of large or small bowel segments may be made which more or less successfully allow continence. Obviously, if it can be effected without compromising the essential surgery, it is preferable to utilize the natural urinary sphincter. This is possible when the primary disease or necessary extirpation, or both, do not involve urinary sphincter action. Limited disease or excisions of the ureters and bladder permit this retention of urinary sphincter action in various diversionary procedures. On the other hand, the disease or its necessary surgical extirpation may frequently involve the urinary sphincter so that its action is a useless or absent factor in voluntary control. In such cases, attempts may be made to substitute an uninvolved rectal sphincter to preserve some comparable degree of urinary continence. This situation, as would be expected, is considerably less satisfactory for very apparent reasons: 1) Any diversionary procedure, which endeavors to substitute the action of the rectal sphincter for the bladder sphincter to preserve continence, must utilize some portion of large bowel immediately adjoining the rectal sphincter[24,48]. Large bowel segments in general have certain disadvantages in diversionary procedures (*vide supra*). These are accentuated because a segment adjacent to the rectal sphincter is essential.

(a) The elected segment of the rectosigmoid above the sphincter is likely to be low in the pelvis, making anastomosis between the ureters or interposed bowel technically difficult.

(b) The natural bacterial flora of the large bowel (particularly the presence of colon bacillus) and stasis predispose to ascending urinary infections at variable times after operation, when ureters are anastomosed to lower bowel segments[18,66].

(c) Absorption of deleterious urinary products from this segment of bowel proximal to the sphincter may reach toxic levels in the blood stream[19,43,57].

(d) The rectal sphincter is teleologically designed to respond to intermittent pressures of solids and gases rather than the single steady increasing pressure of fluids as is the case with the bladder sphincter.

However it may be, the intimati n

here is that, all things considered, endeavors to substitute rectal sphincter action for the natural genitourinary sphincters, are in the main inadequate. They appear even less worthy of emphasis in view of the fact that leakage and skin irritation, incident to diversion techniques where urine is continuously discharged without sphincter action, can be very satisfactorily controlled by properly adapted collecting devices (for example, Koenig-Rutzen bag).

But, there are those instances in which it is impossible because of the involvement of primary disease or its indicated excisions to preserve any natural sphincter action, urinary or rectal. The sphincteric structures upon which continence depends, are either not present or not functional. These are practically always instances of very extensive disease where very wide excision of the urinary tract and other tissues is indicated. They constitute the second category of urinary diversion procedures, those in which there can be little or no voluntary control of urinary flow. This is true because despite many ingenious attempts, experimentally and clinically, no diversionary procedure has been devised which allows any appreciable continence when sphincter action, urinary or rectal, cannot be utilized.

The question of preservation of urinary continence remains, in the minds of many, fundamental in the selection of any of the now possible diversionary procedures for various disorders where urinary diversion of one kind or another is essential. There is some reason for it. Voluntary control of urine flow is quite obviously desirable if it can be achieved without jeopardizing the ultimate objectives. But the overall objectives in the performance of any surgical procedure in which urinary diversion is indicated are not to be sacrificed or compromised simply to preserve variable or doubtful degrees of urinary continence. This is apparent when the indications for urinary diversion are compared with the procedures by which it can be accomplished.

CURRENT INDICATIONS FOR URINARY DIVERSION PROCEDURES. It has already been stated above that the indications for urinary diversion procedures have in general remained the same, but that the means of their accomplishment have been considerably advanced.

The indications, it will be recalled, were broadly stated: impending or actual urinary obstruction, promotion of healing, and the reduction of persistent pain. All of these indications may arise singly or severally from a variety of primary causes.

Generally categorized, these primary causes are: congenital anomalies, trauma, inflammation, metabolic disorders or new growth[1,2,32,63,66]. All of these primary causal agents in their diverse forms are capable of producing acute or chronic lesions of the urinary tract which destroy or obstruct its continuity, heal slowly, or are persistently painful. Depending upon their particular nature, some form of temporary or permanent urinary diversion may be indicated. They are briefly mentioned here as a reminder of a wide variety of disorders where diversionary procedures may conceivably be essential in management.

With congenital anomalies of the urinary tract, the malformations to be corrected are usually obstructive or fistulous and when these cannot be primarily repaired, then by-pass or excision, or both must be carried out with reconstitution of the channels by current diversionary procedures[32].

When extensive trauma is the primary cause or indication, diversion of the urinary flow is usually necessary to promote healing and reduce severity

of pain. The shunting of the urinary stream away from the injured site accomplishes both. But in most cases, the simple long standing diversionary procedures (for example, cystotomy) suffice and the newer techniques for the same purpose are neither needed nor indicated. There are exceptions, such as those in which the trauma has been so extensive that the normal urinary channels have been damaged beyond any limits of repair and some more complicated diversionary technique must be permanently substituted. These instances are occasionally encountered[14].

Conditions causing primary inflammation of the urinary tract are very numerous. In the main, these are usually transient and for the most part yield to conservative measures of treatment. They seldom require consideration of urinary diversion to reduce or eliminate them.

More frequently the inflammatory or infectious processes of the urinary tract where diversion must be considered are concomitant to other more serious primary disorders, such as malignancy and its infectious or inflammatory complications[29].

Metabolic disorders, such as those resulting in formation of the urinary calculi, very rarely require consideration of the recently developed urinary diversion procedures to relieve obstruction, promote healing or alleviate pain. In these instances, the performance of the simple long standing and familiar procedures is almost invariably adequate (for example, cystotomy, ureterostomy)[14].

In by far the great majority of instances, the recently developed diversionary procedures are indicated and undertaken to relieve the obstruction, promote the healing and relieve the pain incident to neoplasms directly or indirectly involving the urinary tract, or to re-establish urinary continuity necessary after their surgical excision. It is within this general category of disorders affecting the urinary tract that recent diversionary procedures have proved of the greatest value and interest. This is true for the reason that their proper application has greatly extended the possibilities of cure or effective palliation in benign or malignant grows involving the urinary channels[7,10,11,13,22,38,41,47,50,55].

Benign or malignant tumors may frequently infiltrate various portions of the urinary tract primarily, or originate from adjacent tissue and encroach upon it secondarily. But, primarily or secondarily, the urinary tract is very frequently involved in the processes of new growth. In these, there are practically always three possibilities relative to palliation or cure so far as urinary diversion is concerned[10,58]:

1) Total excision of the growth and reconstruction of the involved portions of the urinary tract by some diversionary procedure.
2) Partial excision of the growth and reconstruction of the excised portions of the urinary tract by diversionary procedures.
3) No excision of growth or the affected urinary tract but diversion of the urinary tract alone away from the involved areas.

Briefly put, urinary diversion may at one time or another be indicated for any condition of primary or secondary neoplastic involvement of the urinary tract. It may provide the means for possible cure, long time palliation or any compromise objective.

There is no question that recently developed diversion techniques have greatly expanded the application of excision procedures in the definitive treatment of tumors which extensively involve the organs of the male and female pelvis. Current diversion pro-

cedures that have been particularly notable in this regard are carcinomatous conditions of the bladder, rectum, cervix and body of the uterus and female vulva[12,59]. In certain of these, prior to the development of current diversionary procedures, the possibility of palliation appeared as remote as cure[47]. Now, however, both objectives are not infrequently attainable. This is accomplished by proper selection of individual cases and the application of the most feasible diversionary procedure. This is for the reason that currently developed diversion procedures have enabled far wider excisions of diseased tissue, and satisfactory restitution of the urinary flow through newly created channels[7,8].

Conditions hitherto considered incurable because of extensive local invasion of large sections of the urinary tract, can now be approached with expectation of long time palliation if not cure. For the same reason, in cases where surgery at best was formerly considered only palliative, cures have been achieved. And in those deemed entirely hopeless for even palliation, astonishing symptomatic relief has been obtained[12]. The general statement may thus be made that recent advances in diversionary technique have considerably increased operability, curability, and palliation in a wide variety of disorders where the disease or its necessary excision primarily or secondarily, involves the urinary tract.

Since the number and extent of malignant and other disorders affecting the urinary tract are considerable and varied, so is the surgery essential to their cure or palliation. Hence, it is that no one of the newly developed diversionary procedures can be universally applied as preferable in all cases. There are, briefly put, many disorders of variable nature and extent, and there are diversionary procedures which can be applied for their treatment. The essential problem is to select the most feasible diversionary procedure possible under the conditions imposed by the disease or its necessary excision, or both.

"Disease + Surgery essential for its Extirpation = Selection of appropriate diversionary procedure to be applied in the individual case." This decision quite obviously is likely to be a matter of considerable judgment and experience. It particularly postulates full knowledge of recently developed diversionary procedures together with their evolution. On this account, the following illustration and summation of various diversionary procedures are presented.

To aid this end, some comment concerning various individual diversionary procedures and their illustrations is in order. Before proceeding to these, some preliminary observations will aid in their clarification:

1) Current urinary diversion procedures are a progressive development or variation of former attempts to adapt different segments of the large and small bowel, technically and functionally, to conduction and excretion of urinary flow to the body exterior.
2) Some, if not all, of the presently favored methods of urinary diversion are, broadly viewed, only variations of procedures attempted many years before.
3) The delay in applying urinary diversion in the past to conditions in which it is now utilized can be accounted for by general advancements in operative technique, physiological knowledge, and development of effective agents for the control of infection.

In brief, almost all of the currently employed diversionary procedures of

the urinary tract had been suggested or carried out long before their present popularity. Failures were largerly due to:[39,43]

a) Imperfect methods of anastomosis between the ureters and the bowel segments which resulted in obstruction to urinary flow;

b) Incomplete knowledge as to absorption from the small and large bowel which allowed toxic products of urinary waste to enter the general circulation;

c) Lack of effective agents to control the ascending infections prone to occur in the urinary tract when connections are made between it and digestive organs (large and small bowel).

With the gradual evolution of refinements in anastomotic technique, increased knowledge in the absorptive characterisics of small and large bowel segments, and the advent of effective broad spectrum antibiotics, many diversionary procedures which were long since devised, tried and abandoned, are now practicable as originally described or in modified form.

In the accompanying illustration and text, the effort has been made to indicate this point. An examination of these will reveal that certain if not the majority of the current diversionary procedures, now recognized and employed with success, were suggested, assayed, and discarded as early as the turn of the century[30,34,43,44,65]. It will also again emphasize the previously cited fact that currently practiced diversionary procedures are largely successful because of refinements of anastomotic techniques, increased knowledge of bowel absorption and the advent of antibiotics for suppression of bacterial infection in the digestive and urinary tract.

In Fig. 1, the effort has been made to represent by line drawings, the diagrams of various urinary diversionary techniques. Body outlines, the essential portions of the urinary tract, and bowel segments, when concerned, are semi-diagrammatically depicted. Not all of the many modifications of various diversionary procedures described in the literature are included. To do so would increase the space and scope of this writing beyond practicality.

Rather a necessary selection has been attempted to portray basic techniques which have been described in the past or modified to current use. Included also as a matter of reference and interest are certain associated names and dates. To conserve space in illustration, more than one of the simpler and earlier diversionary procedures are indicated on a single panel (Panels 1, 2 and 3). In the more complicated, more recently developed and currently employed techniques, the entire space of a single panel has been necessary for the representation of each individual procedure (Panels 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20).

PANEL 1. *Cystotomy:* the suprapubic opening of the bladder to the body exterior.

This is one of the earliest described procedures for urinary diversion (Franco, 1556)[34], also one of the safest and most familiar. It is still in wide current use as a diversionary procedure in urethral obstructions (prostatic or other) and in urethral injuries as a temporary or permanent measure. Its obvious disadvantages are skin irritation incident to leakage of urine and lack of control of urinary flow.

PANEL 1. *Nephrostomy:* the opening of the kidney pelvis to the exterior at the body flank.

This is also one of the earliest described of urinary diversonary procedures and one of the most familiar. It is still widely and currently used in instances of urethral obstruction or

destruction where one of the more recently developed diversionary techniques cannot be applied (extensive locally invasic malignancy), also as a temporary decompressive measure following the extraction of renal calculi. Disadvantages are those of cystotomy: skin irritation incident to urinary leakage and absolute lack of voluntary control.

PANEL 2-A. *Cutaneous ureterostomy:* ureter or ureters transplanted to skin of external body surface (abdomen).

An early devised and still not an infrequently utilized diversionary procedure employed in instances of destruction of the bladder or lower ureter, or both, incident to trauma, inflammation or new growth. Disadvantages are difficulty in preventing urinary obstruction regardless of how careful the technique. In addition, there is always skin irritation of some degree due to leakage and complete lack of voluntary control. For these reasons, cutaneous ureterostomy is rapidly being replaced by more recently developed urinary diversion techniques, such as that described by Bricker as the "ileal conduit" (*vide infra*).

PANEL 2-B. *Ureterovesicular transplantations of the ureter (or ureters).* Transplantation of the ureter (or ureters) from their natural sites of emptying into the bladder to another bladder location.

A diversionary procedure long ago and still currently practiced. In almost every instance, the indication for its use is the inadvertent transection of one or both ureters incident to extensive pelvic surgery (for example, panhysterectomy). The sectioned ureter is re-anastomosed to the bladder at a site different from its natural bladder orifice, largely because this procedure under most circumstances is easier technically than anastomotic union of the cut ends of the ureter (ureteroureterostomy). Successfully performed uretero-vesicular transplantation of the ureters is satisfactory because there is little disturbance in the urinary flow by such diversion. Voluntary control is maintained through a normally functioning bladder whose sphincter action is preserved. Occasionally this procedure is applied in conditions where the bladder can still be utilized in spite of neoplastic involvement.

PANEL 3-A. *Uretero-ureterostomy:* end of ureter of one side to side of ureter opposite. This type of ureteroureterostomy is not to be confused with uretero-ureterostomy where the cut ends of the same ureter are anastomosed (ipsolateral uretero-ureterostomy). Contralateral uretero-ureterostomy (as shown), is the anastomotic joining of the cut end of one ureter to the side of the intact ureter on the side opposite.

This procedure, though relatively early utilized and described, is now rarely employed. Indications for its use are generally those previously mentioned for uretero-cystotomy; that is to say, where one ureter has been inadvertently transected during pelvic surgery or in instances where a single ureter has been obstructed or destroyed in past by trauma, inflammation or neoplasm. Contralateral uretero-ureterostomy on the whole is not a satisfactory procedure because of the technical difficulties in making and maintaining a satisfactory permanent anastomosis. Bladder function and voluntary urinary control are maintained through the normal outlet, but obstruction of urinary tract is likely, with ensuing hydronephrosis on the side of the sectioned ureter. For this reason, it has been largely supplanted (*vide infra*) by uretero-ileo-cystostomy.

PANEL 3-B. *Cystorectosigmoidostomy* (Maydl, 1894)[46]. Anastomosis of the bladder above the trigone to the recto-

sigmoid colon, thus creating a passage, fistula or shunt of urinary flow from the bladder to the large bowel (rectum).

Originally devised as a procedure for the relief of neoplastic obstruction of the urethra incident to neoplasm of the bladder or prostate, which allowed urinary flow to pass and be excreted through the rectum, this procedure had the advantage of substituting the action of the rectal sphincter for that of the bladder in achieving some voluntary control of urine. But, because of almost inevitable ascending urinary infection by contamination of the bladder with colon organisms, it was soon abandoned. It is chiefly of interest because it represents an early forerunner of certain currently employed urinary diversionary procedures. It is one of the initial attempts to divert urinary flow to the body exterior via anastomosis with a segment of the bowel or gastrointestinal tract.

PANEL 4. *Bilateral uretero-sigmoidostomy:* anastomosis of the ureters to the sigmoid, or rectosigmoid colon. First described by Mauclaire, 1894[44], in its essential features, but actually widely exploited, modified, and popularized by Coffey in 1904.

It is recalled as the outstanding prototype of many modern urinary diversion procedures. This is because it was the first attempt at direct juncture (anastomosis) between the ureters and bowel segment. At the time it was attempted and described, technical methods of anastomosis of ureters to bowel were by modern standards quite crude. Further, the absorptive capacities of the large (or small) bowel for deleterious urinary products were incompletely appreciated. More than this, there were few measures to control effectively the infectious processes prone to occur in the urinary system when joined to the heavily contaminated hollow viscera of the digestive tract. Still, in spite of this, uretero-sigmoidostomy as originally described by Mauclaire and emphasized by Coffey[15], had enough success to warrant continued use and modification according to the various conditions which the procedure was designed to relieve. These conditions were in the main malignant obstructive or destructive processes, primarily or secondarily involving the urinary tract (ureters and bladder), in which the procedure was carried out as a palliative procedure with the diseased organs left *in situ* or only partially excised. The urinary stream was simply diverted away from the involved portion of the urinary tract into the sigmoid colon, by an anastomosis of the ureters to the large bowel. In the original technique, action of the rectal sphincter was preserved and therefore a considerable degree of urinary continence, the subject voluntarily voiding urine and feces through the rectum at the same time. Of the original Coffey procedure, there were many modifications. These came about largely for two reasons:

a) Colostomy of one type or another was frequently necessary in conjunction with urinary diversion because the disease process frequently involved the lower bowel as well as the urinary tract and,

b) recognition of the fact that the inevitable ascending infection (pyelonephritis) attendant upon uretero-colonic anastomosis, was directly related to the fecal content of the bowel to which the ureters were joined. Thus, attempts were made to direct the fecal content away from this segment.

Many variant procedures or modifications have been employed and described: (Panels 5, 6, 7, 8, 9, 10, 11, 12) from that time to the present.

PANEL 5: *Uretero-sigmoidostomy with sigmoid colostomy in continuity*[15].

A simple variant of the Coffey pro-

cedure, allowing partial diversion of the fecal current. Rectal sphincter is preserved but continence to both urine and feces are only partial because of leakage of both through the proximal colostomy in continuity. There is very little or no effective diversion of fecal content away from the anastomotic segment of ureters to bowel.

PANEL 6. *Uretero-colostomy with the sigmoid colostomy completely diverting* and the distal large bowel segment left defunctionalized *in situ*[9].

This is the so-called "wet" colostomy, a procedure still in current practice. The fecal and urinary streams are both voided through the common stoma of the permanent diverting colostomy. The technique may be, and frequently is, combined with resection of the distal colon segment and any or all of the remaining pelvic viscera (pelvic exenteration). In such exenteration cases[6,7,12], it is frequently an alternate choice to other diversionary techniques such as cutaneous ureterostomy or the "ileal conduit" operation (*vide infra*). The wet colostomy has familiar and obvious disadvantages. The fecal stream is not removed from the site of the uretero-colic anastomosis which predisposes to ascending urinary infection. There is no continence of urine or feces so that external skin soilage is great and requires constant care. This technique is rapidly being supplanted by the more recent "ileal conduit" procedure.

PANEL 7. *Uretero-sigmoidostomy* with *proximal defunctionalizing colostomy* (Latheisen, 1899)[60].

As will be noted from the illustration, this procedure consists in the anastomosis of the ureters to the distal closed portion of the rectosigmoid after the performance of a proximal permanent, completely diverting, colostomy. The rectal sphincter is therefore preserved, so that urinary and fecal flow have a common repository and sphincter (rectal). There is control of urine and feces, these being jointly voided by rectal sphincter action. The fecal current is completely diverted from the uretero-sigmoid anastomotic segment so that ascending infection of the urinary tract should, at least theoretically, be less. The procedure obviously postulates leaving the rectosigmoid bowel *in situ*, and is a possibility in instances where disease has destroyed or obstructed the lower ureters and bladder, but left the sigmoid and rectum relatively intact. There is also the usual disadvantage of incontinence to feces and skin soilage associated with any completely diverting permanent colostomy.

PANEL 8. *Uretero-sigmoidostomy with ureteral anastomosis to the distal, completely separated rectosigmoid segment*, with that segment and the proximal sigmoid brought out through the preserved rectal sphincter (Gersuny, 1898)[53].

This is a complicated attempt to achieve the objectives: complete separation of the uretero-colonic segment from the rest of the large bowel (to reduce the possibility of ascending urinary infection), and voluntary control of urine and feces by utilization of the rectal sphincter. Although technically feasible, unavoidable surgical injury to the sphincter and the presence of an additional bowel lumen brought through a space intended for the rectum, alone makes its use impractical. Thus for the reason that voluntary control is lost as a result of injury to the musculature or innervation of the rectal sphincter in performance of the procedure, the sphincter, because of poor or no function, acts as an obstruction to the passage of both urine and feces.

PANEL 9. *Uretero-sigmoidostomy to a separated sigmoid pouch with anas-*

tomosis of the sigmoid pouch to the rectum and re-establishment of large bowel continuity by end to end anastomosis of the large bowel segments across the deficit left by the formation of the sigmoid pouch (Muscatello, 1904)[34].

This procedure accomplished a relative isolation of the bowel segment to which the ureters were anastomosed from the fecal current of the large bowel. The urine accumulated in a relatively feces-free large bowel segment which then drained into the rectum, which in turn was in direct continuity with the rest of the large bowel. The rectal sphincter thus controlled simultaneously the flow of urine and feces which were voided simultaneously through the rectum. Theoretically and practically an improvement, but inevitably attended by ascending urinary infections and toxic absorption of urinary products.

PANEL 10. *Uretero-rectosigmoidostomy with end-to-side sigmoid rectosigmoidostomy* (Decomps, 1909)[34].

This procedure was essentially a less complicated variant of that immediately described (see above, Panel 8). Urine and feces were simultaneously voided through the common channel of the rectum and the voluntary control of the rectal sphincter. The fecal stream was diverted away from the site of the urethral anastomosis, though not as completely, and ascending urinary infections were likewise common.

PANEL 11. *Formation of a separate cecal pouch preserving the appendix intact with uretero-cecostomy, ileocolostomy* to re-establish continuity between small and large bowel, *and cutaneous appendicostomy* to allow exit of of the urine from the cecal pouch to the abdominal exterior (Verhoogen, 1905)[67].

In this procedure, there is no connection with the rectosigmoid segment of the colon and hence no voluntary urinary control. The unique feature is the use of the preserved appendix as the ultimate conduit of urine from the formed cecal pouch to the exterior. It is a prototype of the much latter and currently employed procedure described by Gilchrist in 1949 (*vide infra*, Panel 18)[27].

PANEL 12. *Formation of a separate ileo-cecal pouch with ureteral anastomosis to its ileal segment, re-establishment of small and large bowel continuity by ileo-colic anastomosis above the disjoined ileo-cecal segment, and anastomosis of the cecal pouch to the recto-sigmoid colon.*

The innovation in this diversionary technique is the anastomosis of the ureters into the terminal ileum portion of the pouch. Theoretically, it has the advantage of removing the ureteral anastomosis to the small bowel, an area less contaminated by the fecal current. It is more easily accomplished and provides a more secure anastomotic site for the ureters. Otherwise, it does not greatly differ functionally from other procedures described above (Panel 9 and 10). Urine and feces are commonly contained in the rectum which is left *in situ*, and discharged together by its sphincter action.

PANEL 13. *Uretero-ileal anastomosis to an isolated ileal segment with ileo-ileostomy of the segment to the terminal ileum whose continuity has been restored by end to end anastomosis* (Nagano, 1901)[34].

This procedure is the prototype of the procedure described by Bricker in 1950 (*vide infra*, Panel 19). It is also one of the archetypes of all diversionary procedures employing ileal segments. While this forerunner technique of diversion has the features of relative simplicity of technical performance and removal of the anastomotic site from direct contact with the fecal cur-

rent, it has one very pronounced fault. This is due to the fact that urine as well as feces, traverse the entire extent of the colon to be commonly voided through the rectum. This long transit of the urine through the terminal ileum and the entire extent of the absorptive surfaces of the colon, allows very great absorption of the contained urine back into the blood stream to reach toxic levels therein. For this chief reason, it is not practicable.

PANEL 14. *Uretero-ileal anastomosis to an isolated ileal segment with anastomosis of that segment to the colon by ileo-cecostomy* (Goldenbury, 1904)[34].

This technique is but a variant of the procedure just described above (Panel 13). The only difference is that the uretero-ileostomy pouch is anastomosed to the cecum instead of the terminal ileum. It suffers the same inherent disadvantage of passing the urinary flow through the entire colon with consequent higher absorption of toxic urinary products before voidance through the rectum.

PANEL 15 A & B. A. *Uretero-ileo-ureterostomy: the interposition of a segment* of ileum to replace a partially destroyed or resected segment of the ureter, between proximal and distal ureteral ends[49].

B. *Uretero-(or pelvo)-ileo-cystostomy:* the interposition of a segment of ileum to replace a completely or almost completely destroyed or excised ureter. The only difference is in the extent to which the interposed ileal segment replaces the ureter. Here it can replace it completely (Pelvo-ileo-cystostomy).

Both of these procedures are of somewhat limited application. They can only be employed where the primary involvement of the disease or its necessary excision is ureteral and the bladder and the urethra are intact. These instances are relatively quite rare. However, the point to be made is that segments of the ileum properly anastomosed can be utilized to substitute for destroyed segments of the ureters in their entire extent from the kidney pelvis to the bladder, unilaterally or bilaterally.

It will be recalled in this connection that short segments of ileum lend themselves particularly well to the function of urinary conduits (*vide supra*). This is because transposition of an anastomosis to them is not difficult. Absorption of toxic urinary products from their lumina in short segments, is not great and their infection (bacterial flora) is considerably less than that of the colon.

PANEL 16. *Bilateral uretero-ileo-cystostomy.* The bilateral transplantation of the ureters to an isolated segment of ileum, this segment in turn being anastomosed to the bladder.

This procedure is but a variant of the preceding (Panel 15). Its use is similarly limited and the procedure can only be employed in those instances where both ureters are destroyed or excised by a process which leaves the bladder and lower urinary tract (urethra) intact, such as perirenal fasciitis. Here the ileum with its single lumen takes the place, in part, of the course of the individual ureters. Control is voluntary through the normal channels (since bladder, urinary sphincter and urethra remain as a part of the channel). Other than this, what has been stated concerning the essential features of absorbability from ileal segments and their bacterial content is the same as for the preceding procedure.

PANEL 17. *Uretero-sigmoidostomy to a separated sigmoid segment with anastomosis of that segment to the urethra and re-establishment of the colon continuity by end-to-end anastomosis* (Emdyne, 1912)[34].

This procedure is an attempt to pre-

serve the urinary flow through the urethra in instances where disease of the bladder (usually malignant) or its necessary excision has left the distal urethra and the rectum intact. The rectosigmoid pouch serves as a bladder with urinary discharge through the urethra. Fecal continence is little disturbed because the continuity of the bowel, from which the sigmoid segment is taken, is re-established by end-to-end anastomosis and the rectal sphincters are intact. But urinary continence is absent, because the bladder sphincter is usually removed along with the bladder. The procedure has the doubtful advantage of an incontinent flow of urine through the urethral orifice. In case that the bladder sphincter can be preserved with any degree of function, there may be some degree of urinary continence.

PANEL 18. *Formation of a separate ileo-cecal pouch with uretero-cecostomy (bilateral to that pouch) and ileocolostomy to re-establish fecal continuity from ileum to large bowel; cutaneous ileostomy of the ileal segment of the pouch to provide exit of the urine to the exterior* (Gilchrist, 1949)[27].

This is one of the most recently developed and one of the most feasible techniques of currently employed techniques of urinary diversion. Since the right colon and terminal ileum are employed for the formation of a separate pouch for the containing and conduction of urine, it has wide applicability. It may be used in instances as a simple bypass, leaving diseased pelvic organs (bladder, uterus, and rectum *in situ*), or ofter their excision with permanent colostomy of the descending or sigmoid colon (pelvic exenteration cases). The cecal pouch substituting for the bladder is of course in direct anastomotic continuity with the ureters but separated from the rest of the colon. The organisms inherent in the colon predispose to ascending infections of the urinary tract, but these can be controlled by the judicious use of modern antibiotics. Absorption from the cecal pouch of deleterious products from the urine diverted into it, is a reckonable factor, but if there is free drainage to the exterior of the contained urine through the ileostomy (formed of its ileal segment), this, too, need not be a contraindicating feature of its use.

There is, of course, no voluntary continence of urine, since the egress of urine is through an abdominal ileostomy devoid of any sphincter mechanism. But with a properly fitting ileostomy bag, soilage and skin irritation are minimal. On the whole, it is a satisfactory palliative or curative adjunct in instances of widespread disease, involving the urinary tract or its excision, or both. It is currently and effectively employed.

PANEL 19. *The so-called "ileal conduit."* Formation of a separate segment of ileum with uretero-ileostomy to that segment and cutaneous ileostomy of its distal end. The distal ileum from which the segment is taken is re-anastomosed end-to-end to re-establish continuity of the fecal stream through the ileum and large bowel (Bricker, 1950)[6].

This procedure is one of the most noteworthy of all currently employed diversionary procedures. It can be simply and easily performed technically. It has wide applicability. Its use of a short isolated ileal segment ensures security of the urethral anastomoses, a minimum of absorption of waste products of its urinary content, and a reduced hazard of ascending urinary infection from fecal contamination. There is no effort to establish voluntary continence of urine, since urinary flow to the exterior is established through cutaneous ileostomy. Skin irritation and soilage are very well controlled by the use of a suitably fitted

collecting bag. Its use precludes few if any excisional procedures, however extensive, on the pelvic viscera of the male and female including the large bowel. It would appear that, with the possible exception of the Gilchrist procedure (Panel 18, *vide supra*), it is the most promising and widely practiced of modern urinary diversion techniques.

PANEL 20. *Formation of a separate isolated segment of ileum with ureteral anastomosis to that segment and anastomosis of the segment to the urethra* (Couvelaire, 1951)[17].

This procedure is a modification of that of Bricker (*vide supra*, Panel 19) in which the urethra is made the channel to the exterior and is therefore limited to conditions in which the urethra is left intact by any disease or excision. Continence of urine depends upon the extent to which the urinary sphincter can be functionally preserved. Practically, it has few if any advantages over the ileal conduit procedure of Bricker.

Regarding the individual diversionary procedures selected above, some additional general comment is at point:

1) The simplest and earliest developed techniques (for example, cystostomy, nephrostomy, uretero-ureterostomy) are still currently and advantageously employed for the simpler disorders of the urinary tract (for example, prostatic obstruction, bladder injury, and others). Further than this, they can be and are applied in more extensive disaffections of the urinary tract when one of the more recently evolved diversionary techniques cannot for one reason or another be utilized. The point to be made in this respect is that these simpler earlier techniques of diversion, which for a long period were the only available safe means of urinary diversion, are being supplanted in a wide variety of conditions by more recently developed diversion procedures. These latter, it may be said, have superseded rather than entirely supplanted them.

2) The diversion techniques currently and widely employed (typified by procedures of Gilchrist, 1949, and Bricker, 1950, *vide supra*), were anticipated many years before their present usage by very similar prototypes. The failure of these earlier diversionary prototype techniques was due generally to the relatively high morbidity and mortality attending their attempted use. More specifically, their failure can be attributed to:

a. Obstruction and leakage at the anastomotic sites incident to imperfections in operative technique.
b. Absorption of toxic urinary products from bowel segments employed into the blood stream in excessive quantities because of incomplete knowledge of the absorptive process in the bowel.
c. Ascending urinary infections because of lack of available antibiotic agents to control the intestinal flora of the bowel segments, utilized in the diversionary processes.
d. Performance of various diversionary procedures in improperly selected poor risk patients as a last resort measure and without adequate preoperative preparation.

But with the gradual evolution, from 1900 to the present time, of refinements in technique, increased knowledge of bowel physiology, availability of powerful antibiotics, and progressive appreciation of the above cited causes of failure, these causes have been gradually overcome. These improvements have thus made practicable in selected instances many of the previously described techniques or their rational modifications.

3. It is obvious that many diversionary procedures are now currently avail-

able for the attempted cure or palliation of diseases primarily or secondarily involving the urinary tract. The essential problem, once urinary diversion has been decided upon for the relief of a particular condition, is the selection of the diversionary procedure best suited to the condition. This selection requires careful consideration in any and every individual case. It is generally predicated upon:

a. *Whether the diversionary procedure is to be performed for palliation or cure*[12,66]. In this regard it is perhaps superfluous to point out that this consideration is largely determined by the nature and extent of the disease. If the case is nearly terminal with no hope of cure, the simplest method of diversion for palliation is undoubtedly the best. On the other hand, if the nature and extent of the disease is such as to present a reasonable possibility of cure or long term effective palliation by extensive excisional surgery and subsequent reconstruction of the urinary tract, then the possibility of use of one of the more complicated currently employed diversionary procedures may be entertained.

b. *The nature and extent of the involvement of the urinary organs, and those which may conceivably be employed as substitutions for them in the diversionary procedure*[8,54]. Thus if the disease primarily involves only the urinary tract proper, leaving the other organs, large and small bowel, free, the diseased areas of the urinary tract may be excised and its function supplanted by one of a number of diversionary techniques employing either large or small bowel. On the other hand, if the disease is such that the organs (large or small bowel) are involved in the disease process along with the urinary tract, then the selection of the diversionary procedure may be considerably restricted: this for the obvious reason that the organs or bowel segments that might be otherwise employed in a given procedure cannot be utilized because they must be excised or bypassed. This situation not infrequently occurs. Exemplary of it is the condition in which a malignant process has involved extensively all the organs of the pelvis, bladder, rectum, sigmoid colon, (uterus, vagina, ovaries and appendages in the female)[6,7,12,50,66]. The indication is for a diversionary process of the urinary tract which allows palliative or curative excision, or if that is impossible, an effective palliative by-pass of the involved area. In this instance, since the large bowel from the sigmoid colon distally is inextricably involved, no diversionary procedure can be employed which utilizes the sigmoid, rectosigmoid or rectum. Because the remainder of the large bowel and the terminal ileum are not a part of the process, the choice of urinary diversion procedure is restricted to some technique employing these available parts (for example, procedures of Gilchrist or Bricker)[8,28].

c. *The presence of other factors limiting choice of diversionary procedure,* such as 1) general debilitation, cardiac, renal, or metabolic disease, which render the subject at best poor risk for any extensive excisional or reconstructive surgery; 2) previous surgical procedures in which portions of the urinary tract have been re-

moved or other organs (segments of large or small bowel) excised, rendering these parts unavailable. Regarding these factors, it is obvious that any diversionary procedure contemplated must be selected with respect to the overall risk against the essential surgery and organs available for the reconstruction[8,20].

Bearing the above considerations in mind, it is apparent that the selection of any particular urinary diversion procedure in the individual case is not a simple matter. No one procedure can be applied in all cases. Each case must be individually considered in its overall aspects. And a rational selection of one of the various diversionary techniques available or possible, can only be made with respect to conditions prevailing in that specific case where diversion is indicated.

Finally, it is perhaps appropriate to re-emphasize the role that the recently evolved and currently practiced urinary diversion procedures have played in advancing surgical treatment in conditions of pelvic malignancy. This is possibly the most important and interesting aspect of the subject.

Demonstration of the fact that, by various diversionary procedures in current usage, the small bowel and to a less extent the large may anatomically and functionally be used to replace ureters, bladder and urethra, has greatly advanced the scope of curative and palliative possibilities. Prior to their evolution and usage, the salvage rate in such instances of advanced malignant conditions was dishearteningly low[34]. This in a large measure was due to such extensive primary or more usually secondary, involvement of the urinary tract that all but the simplest surgical methods for relief (cutaneous urethrostomy, nephrostomy, and others) were considered futile. Moreover, extensive excisions for possible cure were frequently neglected because of necessary excision of what were considered essential portions of the urinary tract. The evolution, advent, and practice of present diversionary techniques have accomplished a very appreciable advance, largely because they have made possible far wider excision of involved tissue of urinary tract or other organs than ever before thought possible. Operability, curability and effective palliation in a great variety of malignant disorders have been gratifyingly bettered thereby[8,12,25,28], and there is much hope that with continued experience and improvement of such diversion procedures, these gains will continue and increase.

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OPHTHALMOLOGY

UNDER THE CHARGE OF

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GLAUCOMA FOLLOWING OCCLUSION OF THE CENTRAL RETINAL ARTERY

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THE characteristic ophthalmoscopic picture of sudden closure of one of the arterial vessels supplying the retina is that of ischemic infarction of the area of the retina supplied by the closed vessel. At times, hemorrhagic extravasations are seen in the infarcted retina; they are usually small and, presumably, result from stasis of the venous circulation or from ischemic damage to the walls of the capillaries. Such hemorrhages complicate the ophthalmoscopic picture but otherwise have no effect on the eye or on its vision. Except in the rare case in which the vessel occlusion has been wholly or largely on the basis of functional vasoconstriction, the vision of the eye remains impaired permanently. However, in the absence of any other preexistent disease process, the ophthalmologist ordinarily does not expect the patient to have any further trouble with the affected eye.

In discussing the possible complications of occlusion of the central retinal artery, Duke-Elder[7] states that some observers have described profuse and massive hemorrhages suggestive of hemorrhagic infarction: "it is probable that they are usually determined by thrombosis in a stagnant vein obstructing the re-established circulation." Duke-Elder[7] adds: "A secondary glaucoma has rarely occurred; in some cases it has been due to inflammatory and neo-vascular changes at the filtration angle, and in others it has been associated with a co-existent venous thrombosis." On the other hand, according to Duke-Elder[7], secondary hemorrhagic glaucoma develops within 3 months of the occurrence of thrombosis of the central retinal vein in such a high proportion of cases, 10% to 20%, that it cannot be incidental. Ophthalmologists are quite familiar with this greatly feared complication of occlusion of the central retinal vein, but it would seem that they have paid little attention to the possibility that glaucoma might develop as a sequel to otherwise uncomplicated occlusion of the central retinal artery. Certainly, until rather recently, articles on this subject have been absent for many years from the literature of ophthalmology. As a result, if acute glaucoma did develop in an eye in which occlusion of the central artery was known to have occurred previously, the observer was inclined to attribute this develop-

ment to a coincidental or secondarily added occlusion of the central vein. The venous lesions were thought to be the dominant factor in initiating the increase in intraocular pressure. Undoubtedly some cases of secondary glaucoma do develop in the manner described by Seidel[22], who, according to Wise[28], "reported the case of a forty-four-year-old female who developed the fundus picture of central artery obstruction, followed in a few days by classic occlusion of the central retinal vein. He saw and followed this woman from the moment of first visual difficulty with no fundus change, through arterial spasm, with fundoscopic appearance of central artery obstruction, to central vein obstruction, hemorrhagic glaucoma, and finally removal of the globe two and one half months later. Pathologically, the eye showed intimal thickening and hyaline degeneration of both the central artery and vein and venous thrombosis at the lamina as well." However, there have been reported by now a number of cases sufficiently well documented to establish the entity of glaucoma secondary to occlusion of the central retinal artery without the addition of the so-called stagnation obstruction of the central retinal vein. That glaucoma does develop secondary to central artery occlusion but much less frequently than secondary to central vein obstruction is supported by the findings of Benedict[2] who noted the occurrence of secondary glaucoma in 41 of 361 thromboses of the central retinal vein (11.4%) but in only 1 of 132 occlusions of the central retinal artery (0.8%).

THE OCCURRENCE OF GLAUCOMA FOLLOWING OCCLUSION OF THE RETINAL ARTERY. In reviewing the literature, Perraut and Zimmerman[19] found that 17 cases of glaucoma secondary to central retinal artery occlusion had been reported by 14 authors between the years 1874 and 1930 and that 9 cases had been described in 7 papers between the years 1950 and 1959. Apparently, no one had written on this subject during the 19 years 1931 through 1949. Perraut and Zimmerman[19] noted also that mention of this entity had been omitted from a number of textbooks of ophthalmology. The diagnosis of primary occlusion of the central retinal artery had been made clinically in all of the 26 cases collected from the literature by Perraut and Zimmerman[19], but definite histopathologic confirmation of the diagnosis was lacking in 10 of the cases. For acceptable confirmation of the clinical impression that the glaucoma, which necessitated enucleation of the eye, had developed as a result of the previous arterial occlusion, Perraut and Zimmerman[19] thought that certain findings were requisite: the occlusion must have been demonstrated microscopically, there must have been histopathologic evidence of ischemic infarction of the retina, the retina should not have shown changes attributable to primary venous occlusion and there should not have been any signs of other possible causes of the glaucoma.

In 1874, Loring[14] and Nettleship[16] each reported a case of embolism of the central retinal artery in which there was a subsequent increase in the intraocular pressure. However, the causative role of the arterial closure in the production of the glaucoma was not definitely established by the findings in the microscopic examination of either eye. Loring[14] suggested that the arterial occlusion in his case might have been due to thrombosis rather than embolism. He noted that the retinal veins were enormously distended, that the arteries were not much reduced in size and that the central artery and vein in the optic nerve were nearly empty. In Nettle-

ship's[16] case, the diagnosis of embolism of the central artery had been made ophthalmoscopically; glaucoma had developed 3 months after the first symptoms. Microscopically, organized clots were present in the trunk and in the two terminal branches of the central artery; the central vein was not found, but edema and hemorrhages were noted in the retina and choroid. In 1875, Nettleship, in association with Watson[26], reported another case in which glaucoma developed subsequent to a clinically diagnosed embolism of the central retinal artery. Microscopic examination of this eye revealed complete occlusion of the central artery. Perraut and Zimmerman[19] considered this to be a histopathologically proven instance of glaucoma secondary to central artery occlusion in spite of the fact that, in one section, the central vein was found to be filled with finely granular cells mixed with a few rust-colored granules suggestive of a probable residual thrombosis of the vein.

After a histopathologic study of 2 eyes, Coats[5] had concluded in 1906: "The evidence therefore does not seem at present to be sufficient to decide whether there is any true causal connection between obstruction of the central artery and glaucoma. On the whole the probabilities are against it, but the decision must be left to future research." Seven years later, Coats[6] described the course of events in a third case. He wrote: "A sudden and complete block first occurred in the main stem of the central artery with arrest of the circulation; in consequence there was formed in the central vein a thrombus which constricted the main lumen and almost completely blocked the inferior temporal branch; subsequently, when circulation had been re-established by the collateral anastomoses, haemorrhage occurred in the distribution of the occluded branch." And he reached the conclusion that there was good evidence that the sequence of glaucoma following arterial obstruction was more than a coincidence and that the glaucoma was not primary in type but was due to inflammation of the iris with the formation usually of a fibrovascular membrane on its surface. He added, however: "It is not impossible that in some cases the factor underlying these inflammatory changes and the glaucoma is a thrombosis of retinal veins occurring while the circulation is in abeyance, and, subsequently, when the circulation is restored, reproducing the conditions which obtain in primary thrombosis of the veins, conditions which are well known to lead not infrequently to glaucoma."

According to Perraut and Zimmerman[19], Leber[13] had at first theorized that the sequence postulated by Coats[6], central artery occlusion—central vein thrombosis—glaucoma, was the most logical explanation of the development of the glaucoma. However, he had been forced to abandon this concept because the microscopic findings in several of the reported cases had failed to support it. According to Benton[3], Opin[17] described his findings in one case of glaucoma secondary to occlusion of the central retinal artery and stated that he had examined microscopically 11 other eyes which had been enucleated because of inflammatory glaucoma following central artery occlusion. In the case which Opin[17] reported in detail, microscopic examination of the enucleated eye revealed that the central artery was occluded just posterior to the lamina cribrosa and that the adjacent central vein was partially occluded by a recent thrombus, supposedly the result of stagnation of blood flow.

Perraut and Zimmerman[19] stated: "We do not believe that secondary oc-

clusive changes in the central retinal vein observed along with the arterial thrombosis in certain cases requires deletion of the case, providing that there was neither clinical nor pathologic evidence that the venous occlusion was primary." These authors stated that, among the glaucomatous eyes which had been sent to the Armed Forces Institute of Pathology, they had encountered a number of eyes in which the glaucoma apparently followed an occlusion of the central retinal artery. They reported the results of their studies of 6 of the more recent cases in which there was clinical evidence that the ocular tension did not become elevated until after the arterial occlusion. They stated that, in these cases, "venous thrombosis was not found, but in two cases the central retinal vein was collapsed. Certainly the retinal picture, both clinically and pathologically, was remarkably different from that characteristic of primary occlusion of the central retinal vein, even in those cases reported as having shown evidence of secondary obstructive endophlebitis." Characteristically, they said, there is "widespread coagulative necrosis involving selectively the inner retinal layers. . . . There is no evidence of old or recent hemorrhage in the posterior segment." In eyes enucleated soon after the occlusion, there is edema of the nerve fiber layer and incomplete disappearance of the ganglion cells, but, in eyes enucleated after a longer interval, there may be shrinkage of the inner retinal layers, complete disappearance of the ganglion cells and an excavated nerve head.

In his 1959 review of the literature on glaucoma, Chandler[4] noted the reports of Wolter and Phillips[32] and of Perraut and Zimmerman[19] on secondary glaucoma following occlusion of the central retinal artery. He wrote: "In all reported cases the central vein showed changes but was not occluded in the sections examined. The changes found in the angle were similar to those usually seen in cases of hemorrhagic glaucoma following occlusion of the central vein. In these cases one must consider the possibility that the vein may have been occluded beyond the area examined."

HISTOPATHOLOGY OF THE ARTERIAL OCCLUSIONS. The nature of the local lesions causing the occlusions of the central arteries in these cases is of some interest and perhaps of some importance. It is recognized that the increased intra-ocular tension of chronic glaucoma may be the precipitating factor in some instances of retinal arterial occlusion. On the basis of his observations in several cases, Otto[18] expressed the opinion that variations in intraocular pressure can initiate spastic constriction of retinal arterial branches with corresponding field defects. Verhoeff[25] studied microscopically sections of the central retinal vessels in cases of chronic glaucoma secondary to lesions in the anterior portion of the globe. He stated: "Secondary glaucoma always produces, sooner or later, endovasculitis of the central retinal vessels, leading ultimately to complete obstruction of both. The same variety of changes are seen as in cases of primary obstruction of these vessels. Thrombosis does not occur. Dissecting aneurisms not infrequently occur in both the vein and artery, producing complicated appearances which have been mistaken for canalized thrombi." In the group of cases under consideration in this review, the arterial occlusions were not induced by increased intraocular tension; but dissecting aneurysms were responsible for the occlusions in several instances, having developed probably in the manner described by Garron[9]. Garron[9] found dissecting aneurysms of

the central retinal artery and its primary branches in 2 eyes, one of which had been removed because of the suspicion of an intraocular tumor and the other because of painful glaucoma. In the first case, the suspected tumor proved to be a subretinal hemorrhage. In the second case, there was subretinal hemorrhage around the disk, but Garron[9] attributed the glaucoma to the keratitis and iridocyclitis which had been observed clinically since there was no evidence of a fibrovascular membrane on the surface of the iris such as is seen in the glaucoma secondary to occlusion of the central retinal vein. Garron[9] thought that, in some cases of atherosclerosis, the fatty infiltration and degeneration led to necrosis of the intima with ulceration of the endothelial lining which permitted the circulating blood to gain access to the stroma of the vessel wall. He wrote, "in cases of hemorrhage and edema around the disc and retina, we frequently suspect central retinal vein occlusion. Rarely, if ever, do we suspect an arterial lesion as productive of hemorrhage. Dissecting aneurysms of the central retinal artery should be kept in mind in the differential diagnosis of retinal hemorrhage adjacent to the disc."

In the case reported by Wolter and Lubeck[31], the central artery in the region of the lamina cribrosa was completely closed by a plug of hyperplastic and detached intima. The central vein was open and filled with blood. There was a new-formed vascular membrane over the peripapillary retina and an extravasation of blood in the posterior vitreous which may have come from the dissecting aneurysm of the central artery. Two short posterior ciliary arteries were occluded also. In the case reported by Wolter and Liddicoat[30], the central artery immediately behind the lamina cribrosa was obstructed by a mass of curled up tissue representing the detached and hypertrophic intima. The central vein was fibrotic, but the lumen was normal. In the case reported by Wolter and Phillips[32], the central artery was completely obstructed by a degenerated mass of curled up layers of tissue, obviously the hypertrophic and detached intima. The central vein all through the removed part of the optic nerve was wide open, but some areas showed extensive lymphocytic endophlebitis and periphlebitis. Two posterior ciliary arteries were completely occluded by curled up hypertrophic intima. The peculiar obstruction of the artery in each of these 3 cases by its own dissected intima was interpreted as the result of a dissecting aneurysm. Wolter and Phillips[32] thought that their case "should convince those ophthalmologists who still think that the arterial occlusion in these cases of secondary glaucoma occurs secondary to venous obstruction that this entity (glaucoma following primary occlusion of the central retinal artery) really exists and that they may see it in their practices." They questioned whether the presence of a dissecting aneurysm in each of these 3 cases was a significant factor in the development of the glaucoma or whether it was merely a coincidence. The latter seems to be the more likely interpretation since other types of obstructive lesions were described in some of the reported cases of glaucoma secondary to central retinal artery occlusion. In Benton's[3] first case, the central artery was completely occluded by a round non-cellular mass with slight calcification; this was interpreted as an embolus from an atherosclerotic plaque in a larger artery. The central artery in the optic nerve was found to be only a strand in the case reported by Holm, Sachs and Wilson[11]; there was considerable endothelial

proliferation of the vein, but there was some blood in the lumen. The lumen of the central artery was closed by a thrombus in the case reported by Winter[27] and in 5 of the 6 cases reported by Perraut and Zimmerman[19]. In Perraut and Zimmerman's[19] sixth case, the occlusion was caused by atheromatosis with hemorrhage into the atheroma. Hemorrhages were present in the globe examined by Winter[27]; but there was no evidence of a dissecting aneurysm, and the bleeding was thought to have occurred during the cyclodialysis which had been performed in an attempt to reduce the intraocular tension.

CLINICAL DATA. Including the cases collected from the literature by Perrault and Zimmerman[19], these authors' own cases and the cases reported by Holm, Sachs and Wilson[11] and by Gupta[10], 34 eyes with glaucoma following occlusion of the central retinal artery are on record. Both eyes of Ross's[20] patient were involved, but the tension of the fellow eye was normal in the remainder of the cases. The ages of 32 patients were stated; 19 were over 60 years old, and only 2 were under 50. There were 18 men and 12 women; the sex of 3 of the patients was not mentioned. Seven of the patients were diabetics and 12, including 4 of the diabetics, had hypertension. Nine of the earlier reported cases were said to have some cardiac lesion. Two patients had had strokes and one developed right hemiplegia 7 months after the retinal arterial occlusion. One patient had intermittent claudication and one had Buerger's disease. There were only 5 patients in whose history no mention was made of the presence either of diabetes or of some type of cardiac or vascular disease. The glaucoma developed within 5 to 9½ weeks after the arterial occlusion in 26 of the eyes (76%); it occurred 10½ weeks after the occlusion in one eye, 3 months after in 2 eyes, 4 months after in 2 eyes, some months after in one eye and 10½ months after the occlusion in one eye. The time interval was not given in one case. Twenty-six of the eyes were enucleated because they were blind and painful; 19 of them within a month after the onset of symptoms and signs of glaucoma. Provocative tests for glaucoma were carried out on a few of the fellow eyes and proved to be negative. There was no evidence of primary glaucoma in any of the eyes included in these reports.

THE PATHOGENESIS OF THE GLAUCOMA. After microscopic study of the anterior segments of 29 globes, in each of which there was a clear record that the obstruction of the central retinal vein had preceded the glaucoma, Samuels[21] stated that "in the causation of the glaucoma that follows occlusion in the central vein there are three anatomic factors to be borne in mind: (1) a disturbance in the blood outflow caused by an obstruction in the main vein, (2) a disturbance in the lymph outflow by a blockage in the efferent pathway by congestion and edema at the nerve head and (3) a disturbance in the aqueous outflow caused by membranes and adhesions at the angle of the anterior chamber." In discussing the possible causes of glaucoma following occlusion of the central vein, Duke-Elder[7] states that there is blockage of the drainage channels at the nerve head and also inflammation at the corneo-iridic angle, produced probably by cytotoxins generated in the damaged retinal tissues, with the formation of extensive adhesions and finally highly vascularized membranes over the entire region of the anterior surface of the iris and the angle of the anterior chamber.

Remarking that the pathogenesis of the glaucoma following occlusion of

the central retinal vein and of that following occlusion of the central retinal artery is not well understood, Perraut and Zimmerman[19] pointed out that, while the histological changes in the posterior segment of the eye are quite different in the two conditions, the changes in the anterior segment are practically identical. The pattern of the histopathologic changes in the anterior segment of the globe has been essentially the same in all the reported cases of glaucoma secondary to central retinal artery occlusion, basically the formation of a fibrovascular membrane on the anterior surface of the iris and on the surface of the trabecula, followed later by the development of peripheral anterior synechiae which close the angle of the anterior chamber. Wolter and Liddicoat[30] wrote: "The nature of hemorrhagic glaucoma following venous occlusion is not completely understood. However, the proliferation of vascular connective tissue in the area of the chamber angle seems to be the direct mechanical cause. Paralleling this proliferation of endothelium and connective tissue in the angle of these cases is the development of thin-walled blood vessels on the anterior surface of the iris (rubeosis iridis). Further development of the disease process often leads to complete angle closure by peripheral anterior synechias." And they added that these changes are also typical of secondary glaucoma following central retinal artery occlusion; they were present in the enucleated eye of their case of secondary glaucoma in which the lumen of the central vein was open and normal while that of the central artery was completely obstructed.

Though most authorities tend to agree that the main cause of increase in intraocular tension in cases of primary occlusion of the central retinal vessels is interference with aqueous outflow by secondarily developed changes in the angle of the anterior chamber, the observations of Vannas and Tarkkanen[24] and of Gupta[10] seem to cast some doubts on the explanation. Vannas and Tarkkanen[24] noted that occlusion of the central retinal vein is prone to develop in eyes presenting evidences of simple glaucoma or at the time of an acute attack of closed angle glaucoma. They found that 42% of 71 patients with central retinal vein occlusion had simple glaucoma and that 9 of 11 patients with unilateral hemorrhagic glaucoma following occlusion of the central retinal vein had simple glaucoma in the opposite eye. They observed that, in cases of rubeosis iridis, the newly formed vessels were seen first around the sphincter of the iris and appeared in the periphery of the iris only where the angle was completely obliterated. They stated: "Peripheral anterior synechiae and vascular membranes have been observed by histological means in the chamber angle after occlusion of the central retinal vein. . . . It would be important to know whether the new formed vessels are formed before or after the acute rise in intraocular pressure. . . . In most cases reported in the literature the rubeosis has been observed simultaneously or after the rise in tension. . . . the fault with the obstruction of outflow in hemorrhagic glaucoma probably lies beyond the visible chamber angle and the synechiae alone cannot account for the elevated tension." In order to determine if possible whether the peripheral anterior synechiae in cases of glaucoma secondary to central vein occlusion preceded the rise of tension or were secondary to the glaucoma, Vannas and Tarkkanen[24] carried out gonioscopic studies on their cases. They concluded: "In eyes where the vein occlusion was not asso-

ciated with simple glaucoma, wide open or only slightly narrow angles were seen. No peripheral anterior synechiae were present. . . . Our findings point toward the secondary role of the visible chamber angle changes in the development of hemorrhagic glaucoma." In the report of his case of secondary glaucoma following occlusion of the central retinal artery, Gupta[10] said that there was no evidence of primary glaucoma in either eye. Acute congestive glaucoma developed 3 months after the arterial occlusion, but the patient refused enucleation of the eye. Five months later, the intraocular tension was 70 mm. Hg (Schiotz) and there were many blood vessels on the surface of the iris and in the angle of the anterior chamber. However, Gupta[10] said, the facility of aqueous outflow remained normal in the affected eye on all occasions.

A case which also might have some bearing on this problem was reported recently by Jensen[12]. His patient, who had not had any symptoms or signs of glaucoma previously, developed acute glaucoma in the left eye 2 days after left carotid arteriography and died 2 days later. Necropsy revealed multiple septic cerebral infarcts. The mechanism of production of the glaucoma was not clear. Histopathologic examination of the globe failed to reveal any anatomic abnormalities in the chamber angle, but showed edema of the corneal epithelium and stroma, lymphocytic infiltration around the vessels of the ciliary body and iris root and edema of the entire ciliary body. Presence of thrombi or contrast medium could not be demonstrated. There were no thrombi, vascular reactions or necrosis in or around the central vessels or in the annulus vasculosus. There was degeneration of the ganglion cells of the retina, which, though possibly a postmortem change, might be interpreted to suggest, at least, a previous functional closure of the central retinal artery.

THE MECHANISM OF FORMATION OF THE VASCULAR MEMBRANES ON THE IRIS. Samuels[21] discussed the mode of formation of the membranes on the anterior surface of the iris and on the chamber surface of the pectinate ligament in cases of obstruction of the central retinal vein. He thought that the membranes were formed probably by the action on the anterior surface of the iris of toxins generated by the disintegration of the recurring hemorrhages and exudates in the retina. He added: "To account for the overwhelmingly vascular element in most of the membranes, it was believed that the walls of the exposed blood vessels at the root of the iris received a stimulus from the toxins in response to which they formed capillaries. This may be likened to the condition wherein the blood vessels lying in contact with the internal limiting membrane of the retina sometimes are seen to react to toxins by sending capillaries forward into the vitreous body."

There seems to be general agreement that, as stated by Perraut and Zimmerman[19], "something provokes an outgrowth of mesenchymal cells from the uveal tissues of the iris root. These cells invade the chamber angle to form a delicate membrane along the inner surface of the trabecula." But it is not known what this "something" is. As noted by Wolter and Liddicoat[30], "The usual explanation of rubeosis and fibrovascular proliferation following venous occlusion, that of development of venous collaterals, is obviously not tenable following arterial occlusion." According to Perraut and Zimmerman[19], Leber[13] thought that, in cases of glaucoma following central artery occlusion, the anterior segment changes were caused by toxic products from

the degenerating retina which were carried to the iris and the filtration angle where the resorption of intraocular fluids takes place, and Opin[17] agreed that the necrosis of the retina produced a toxin which was carried to the chamber angle by the intraocular fluids. Coats[6] thought that products of the breaking down of hemorrhage might cause the changes in the iris and in the spaces of Fontana. However, this theory is not tenable as, in a number of the involved eyes, histopathologic examination failed to reveal evidence of intraocular bleeding.

It is well-known that rubeosis iridis occurs not infrequently in association with proliferative retinopathy in patients with diabetes mellitus and is followed or accompanied by the development of secondary glaucoma. It is thought by some to be characteristically diabetic. Fralick[8] reported his studies of 5 cases of secondary glaucoma in which rubeosis iridis was present. Three of the patients were diabetics and 2 non-diabetics. He commented: "In all of the cases presented herewith, the only common feature was the obvious circulatory disturbance to the degree that rubeosis iridis and hemorrhagic glaucoma developed. The writer, therefore, cannot support the contention that rubeosis iridis is a manifestation of an ocular syndrome seen in its true form only in diabetics. It is his belief that, given the right pathologic vascular supply to the eyeball, metabolic abnormalities will be established to promote a low-grade iritis with new-vessel proliferation and secondary peripheral-root synechiae, resulting eventually in hemorrhagic glaucoma."

One wonders whether, in cases of central artery occlusion as well as in cases of central vein occlusion, hypoxia of the retina may not be the primary factor in producing the metabolites which stimulate the formation of the neovascular membranes. It is perhaps noteworthy that, in some of the cases with secondary glaucoma, short posterior ciliary arteries were found to be occluded as well as the central artery. Redmond Smith[23] suggested that, possibly as a result of anoxia of the retina induced by central vein occlusion or other causes, "a metabolite is produced which stimulates new vessel formation. This metabolite may thus give rise to a rete mirabile or the convoluted vessels often seen on the optic disc after central venous occlusion. . . . The metabolite may however act vicariously on the iris, producing a neovascular membrane which may occlude the filtration angle and cause thrombotic glaucoma." He stated that gonioscopic observations showed that neovascularization of the iris precedes thrombotic glaucoma, and that, when glaucoma first develops, a part of the angle is usually normal. The studies of Vannas and Tarkkanen[24], which were referred to earlier, did not entirely confirm these observations. Redmond Smith[23] and Wise[28] both agreed with Fralick[8] that there is no difference between diabetic and postvenous thrombotic rubeosis iridis. Wise[28] thought that venous obstruction was probably the most important, though not the only, factor in the development of rubeosis iridis.

In discussing the formation of new vessels in the retina and vitreous following occlusion of the central retinal vein, Ashton[1] stated that he had found, in pathologic specimens, that vascular proliferations into the vitreous were associated always with underlying areas in the retina of obliterated capillaries or obstructed veins. He commented: "Here it may be suggested that the vasoformative factor is elaborated in the hypoxic retinal tissue, and, failing to drain away, seeps into the vitreous where it reaches a concentration suffi-

cient to stimulate the vessels to grow inward. . . . The concept of a preformed factor diffusing through the vitreous is applicable also to the problem of neovascularization of the iris. It is certainly not without significance that new vessels on the iris so frequently follow the development of retinal disease, wherein the pattern of vascular involvement provides the conditions for production of the vasoformative factor . . . the vasoformative factor may be elaborated either in the hypoxic retina or by fibroblasts in the vitreous and be carried forward to stimulate the growth of vessels anteriorly." Redmond Smith[23] thought that his findings indicated that eventual reestablishment of the retinal circulation by neovascularization of the disk might result in arrest of the progress of the rubeosis iridis. Possibly, as suggested by Ashton[1], the vasoformative factor is drained away by the new-formed vessels before it can accumulate in sufficient amounts to reach the iris.

According to Wise[29], Michaelson[15] thought that retinal vascular development in the fetus occurred in response to some unknown tissue factor present in areas of relative anoxia of the retina and that the ability of the veins and capillaries to form new vessels is not lost after birth but only lies dormant. Wise[29] postulated that circulatory stagnation resulting from venous obstruction would produce a state of relative retinal anoxia distal to the obstruction and reactivate the vasostimulating factor of Michaelson[15]. New vessels would then grow out into the hypoxic area to restore the circulation and provide adequate tissue oxygenation. In explanation of the relative infrequency of neovascularization in cases of arterial obstruction, Wise[28] commented: "In arterial obstruction an anemic infarct occurs, and tissue death, destruction and absorption ensue. The tissue in which factor x (the vasoformative substance) would ordinarily develop disappears before the stimulant for neovascularization has been present long enough to exert its influence. This is substantiated by the extreme clinical rarity of neovascularization after arterial obstruction. Collaterals or neovascularization due to arterial obstruction should occur only in those cases of prolonged partial obstruction. In such cases, the partial anoxia is sufficient to stimulate the production of factor x, but not to produce tissue death."

In cases of pulseless disease, neovascularization of the retina does occur in the somewhat abortive form of peripapillary arteriovenous anastomoses and microaneurysms. Wise[28] thought that, in this disease, as the degree of arterial obstruction progressively increased and the blood supply became gradually more and more inadequate, the retinal tissue would sooner or later become sufficiently hypoxic for the beginning of production of the vasoformative substance, but not sufficiently anoxic, at least for a time, for active tissue metabolism to be stopped. If this theory is correct, then, in some instances, the vasoformative substance must accumulate in sufficient amounts to diffuse through the vitreous and stimulate the new growth of vessels on the anterior surface of the iris, for rubeosis iridis has been observed clinically in cases of pulseless disease. A similar process might readily explain the development of rubeosis iridis following retinal arterial obstructions of other types, the only requisite being the preservation of sufficient living retinal tissue to provide for the accumulation of the vasoformative substance as one of the products of anaerobic metabolism.

Summary. Acute congestive glaucoma has been observed to follow within several weeks primary occlu-

sion of the central retinal artery in previously non-glaucomatous eyes. No symptoms or signs of chronic glaucoma have been present in the fellow eye in these cases. Careful histopathologic studies of a number of enucleated globes have confirmed the existence of the entity of glaucoma secondary to occlusion of the central retinal artery not complicated by obstruction of the central retinal vein. The interval between the arterial occlusion and the onset of glaucoma is shorter usually than that between occlusion of the central vein and so-called hemorrhagic glaucoma. The glaucoma is intractable and resistant to miotics and to surgical measures for reducing the intraocular tension. Enucleation of the eye is necessary in most cases for the relief of pain.

The changes seen microscopically in the anterior segment of the globe which seem to be responsible mechanically for the elevation of the intraocular pressure are practically identical whether the preceding vessel occlusion has been venous or arterial. There must be, therefore, a common exciting cause for the development of these changes. The nature of this common cause has not been determined definitely as yet. There is some evidence, however, in favor of the possibility that hypoxia of the retina and the consequent reactivation of the vasoformative factor of Michaelson[15] may be responsible for the new growth of vessels and the formation of fibrovascular membranes on the anterior surface of the iris and in the angle of the anterior chamber. If retinal hypoxia is actually the essential factor in its development, then glaucoma should be more apt to occur in the event that the entire retina is not infarcted since the presence of living retinal tissue is necessary for the continuation of anaerobic metabolism and the production of the vasostimulating substance.

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PROCEEDINGS OF

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Recent Developments in the Structure and Function of Bacteriophage. THOMAS F. ANDERSON, PH.D. (The Institute for Cancer Research, Philadelphia 11, and the Division of Biology, University of Pennsylvania, Philadelphia 4, Pa.). Recent high resolution electron micrographs show bacteriophage T_4, "negatively stained" with phosphotungstic acid, to be very similar to T_2 as seen by S. Brenner and R. W. Horne (The London Times Science Review, Autumn 1959 p. 10). The 20 Å thick polyhedral head membrane containing the DNA is attached to a narrow neck surrounded by a thin collar. The shaft of the tail possesses cross striations spaced 35 Å apart and terminates in a hexagonal base plate containing six symmetrically placed pins to which extremely thin long fibers are attached. When the tip of the tail encounters a bacterial host cell wall, the tail sheath contracts to expose a needle (F. Kellenberger and W. Arber, Z. Naturforsch. **10b**, 698, 1955) which measures 70 Å in diameter which apparently penetrates the cell wall. The needle has a 25 Å hole running through its center through which the DNA of the phage is presumably delivered to the host's protoplasm.

Once it has performed its function of delivering the DNA to the host cell the protein coat is disposable (A. D. Hershey and M. Chase, J. Gen. Physiol. **36**, 39, 1952).

The injected DNA, which had been metabolically inactive up to now, quickly reorganizes the bacterial syntheses for the production of phage. It directs the synthesis of at least five new enzymes concerned with the synthesis of its peculiar DNA which contains glucosylated hydroxymethylcytosine (J. G. Flaks and S. S. Cohen, Biochim. et Biophys. Acta, **25**, 667, 1957 and S. B. Zimmerman, S. R. Kornberg, J. Josse, and A. Kornberg, Fed. Proc. **18**, 359, 1959). Some 10 minutes after infection, phage DNA begins to aggregate within the host's cytoplasm in the form of head-shaped packets (E. Kellenberger and A. Ryter, J. Biophys. Biochem. Cytol. **4**, 323, 1958) which then aggregate about themselves the various protein elements whose syntheses have likewise been specified by the phage DNA. The first mature phage particle appears about 12 minutes after infection and synthesis continues for 20 or more minutes. Infected cells then begin to lyse and each liberates 100 or more mature particles. The DNA packets they contain can remain metabolically inactive for years until their protein coats or "capsules" (A. Lwoff, T. F. Anderson and F. Jacob, Ann. Inst. Pasteur, **97**, 281, 1959) deliver them to host cells to initiate further cycles of bacteriophage synthesis.

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The Metabolism of Chromosomes*. GEORGE T. RUDKIN (The Institute for Cancer Research, Philadelphia 11, Pa.). The metabolic patterns of the two functions of the chromosomes, replication for maintenance of the continuity of germ plasm and control of cellular metabolism, must apply at the level of individual gene loci. Of the four main constituents of chromosomes, DNA is currently thought to carry the specificity of the genes and RNA to mediate the transfer of the specific form of a gene to protein. The functions of chromosomal proteins (histones and non-histones) have not been crystallized into a coherent theory, although the histone fraction is quantitatively correlated with DNA. Measurements of the DNA and RNA contents of active regions of giant chromosomes, the so-called "puffs," are presented and found to be consistent with the DNA-RNA theory of gene action.

In a puff region of a chromosome of *Rhynchosciara angelae*, DNA was found to quadruple while in neighboring non-puff regions it only doubled. It is concluded that the DNA content of a gene locus, expressed per chromosome, is not necessarily a constant. The variability in the DNA content of whole nuclei superimposed on a constant mean value may have significance with respect to gene action. The data also indicate that chromosomal participation in cellular metabolism can take place simultaneously with replication. If disproportionate synthesis were to take place in actively dividing cells, then a daughter cell would not be expected to have exactly the same amount of DNA as its parent. Since the disproportion was observed in only about one fiftieth of the total chromosomal material in Rhynchosciara, it would have not been detected by existing methods for measuring total nuclear DNA. Similar arguments may be developed with regard to disappearance of the "extra" DNA, observed by Stich and Naylor in another species.

A puff in a *Drosophila melanogaster* chromosome was found to be rich in RNA but to have the proportionate amount of DNA. Both types of puff, "RNA" type and "DNA" type, are found in the same chromosome in some species and there are indications in the literature that still different metabolic patterns are found as well. The wide variety of metabolic patterns found within chromosomes is interpreted as a reflection of the differences between genes, here expressed in the genetic material itself.

Accurate and reproducible timing of the occurrence of puffs suggests an interrelationship between the metabolic activity of specific chromosome regions and the physiological state of the whole organism. Most of the known regions become puffed at or close to a critical period in the metamorphosis of the insect such as one of the larval moults. The possibilities that specific loci react to the presence of humoral agents and that their products in turn are instrumental in influencing synthetic activity in other cell types provide inspiration for future research into the physiology of chromosomes in development.

Some Nucleo-cytoplasmic Relationships in Tissue Culture Cells and Amebae. LESTER GOLDSTEIN, PH.D. (Division of Biology, University of Pennsylvania). In order to establish whether or not current views on the relation between DNA, RNA, and protein are valid, the incorporation of tritiated cytidine into the nucleic acids of

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human amnion cells established in tissue culture was studied. Current hypotheses hold that RNA must be synthesized in the nucleus (by the genetic material) and then transmitted to the cytoplasm where RNA may act as a template for protein synthesis. It has been demonstrated, in the experiments reported here, that the RNA of the nucleus incorporates tritiated cytidine before the appearance of any label in cytoplasmic RNA. If at this time the unincorporated radioactive precursor is removed from the cells, the degree of label in the nucleus slowly diminishes while the label in cytoplasmic RNA increases. Thus, it would appear that nuclear RNA may be a precursor of cytoplasmic RNA, a possibility consistent with the hypothesis stated above. Similar experiments, carried out with greater precision, suggest that the RNA of the nucleus is synthesized in the chromosomal material and is then transferred to the nucleolus, where it is localized for a period of time during which some unknown processes must be carried out.

In order to study the behavior of the proteins of nuclei, experiments were carried out with *Ameba proteus*. Protein-labeled (C^{14} and S^{35}) nuclei were grafted (by micromanipulation) from radioactive amebae to non-radioactive amebae. By means of autoradiography it was possible to determine that the protein moved from the nucleus to the cytoplasm and then returned rapidly to the nucleus, where it is largely localized. This is quite a unique observation and experiments are now in progress to determine the possible significance of this rapidly migrating protein which is so obviously concerned with nucleo-cytoplasmic relationships.

BOOK REVIEWS AND NOTICES

PRÉCIS DE DERMATOLOGIE. By B. DUPERRAT, Hôpital Saint-Louis, Paris. Pp. 1,106; 565 ills. Paris: Masson et Cie, 1959. Price, 19.200 fr.

As would be expected from the author of this volume, it is a most comprehensive compilation of practically all the common dermatoses plus a number which are less common. They are treated in a systematic fashion, with an extensive table, and beautifully illustrated by black and white photographs and by a number of line drawings. The line drawings, especially those dealing with the bullous dermatoses, are outstanding. In keeping with the author's interest in dermatopathology, there are more than the usual number of good photomicrographs of histologic sections. The material covers many American, as well as French and other works. Unfortunately, there are no bibliographic references to the numerous works mentioned in the text. While the terminology is not always that which is used in English, for instance, the group known as parakeratoses, the material is unusually up-to-date, for example, the Sneddon-Wilkinson subcorneal pustulosis is given appropriate space. The work is divided into two parts: the first deals with the diseases of the skin from the standpoint of morphology; the second deals with the processes classified according to cause. This is topped off by a formulary and an extensive index. The three shortcomings of this volume for the American reader will be: its size (the work is rather heavy physically); the fact that it is written in French, and the price. However, for the genuine student of dermatology this book will be a valuable adjunct to his ready sources of reference. H.B.

MANUAL OF SKIN DISEASES. By GORDON C. SAUER, University of Kansas School of Medicine. Pp. 269; 151 ills. Philadelphia: J. B. Lippincott Co., 1959. Price, $9.75.

THIS is a unique contribution to the smaller books on cutaneous diseases, stimulated by the request of a medical student for a good 50-page book on dermatology. The author has produced a volume considerably larger than the 50 pages (269), in the compilation of which he has embodied a number of original features. Among these are: (1) Numerous line drawings, not only in the text but on the back of the cover and fly-leaves; (2) 28 color plates of outstanding quality; (3) black and white photographs with explanatory diagrams pointing out the salient features of the dermatoses under discussion; (4) text which is "compact, concise, and concrete" as stated on the dust cover; (5) blank pages in the dermatologic formulary for the owner of the book to insert his favorite prescriptions.

This volume consists of two distinct but complementary parts: The first part contains the chapters devoted to the diagnosis and the management of the important common skin diseases. The second part consists of a very complete dictionary-index to the entire field of dermatology, defining the majority of rare diseases and the unusual dermatologic terms. The index is also illustrated, a rather unusual technique.

The contents are of wide range, including, among other items, structure of the skin, laboratory procedures and tests, dermatologic diagnosis through various types of dermatoses, skin and internal disease, tumors of the skin, and basic dermatologic equipment. Although this book is intended for the medical student or practitioner, it is useful to all physicians including specialists who wish a quick review of dermatology. It is really a new departure in the small book field on dermatology.

H.B.

TEACHING COMPREHENSIVE MEDICAL CARE. By KENNETH R. HAMMOND, PH.D. AND FRED KERN, JR., M.D., Behavior Research Laboratory and School of Medicine, University of Colorado. Pp. 642. Cambridge, Massachusetts: Harvard University Press for The Commonwealth Fund, 1959. Price, $10.00.

THIS is a highly significant publication in the field of medical education for it details the results of an extensive program of measurements of a medical educational experiment. Dr. Hammond and his fellow psychologists at Colorado University have made a real contribution by their pioneer efforts in the area of measurements of educational efforts. The techniques they developed will provide a much-needed foundation for further studies of the many facets of the educational process.

Unfortunately the educational experiment in comprehensive care that was measured

was not truly comprehensive. Four early chapters consist largely of a projection by the staff of the failures in the program upon the patients. These were tried and often found guilty of being old, poor, uneducated, unreliable, uncooperative, ungrateful people whose problems were often not the clear-cut, textbook biological disorders. The staff and students report becoming frustrated and angry at many of these patients, and then wondered at the number of broken appointments. Somewhat surprisingly, the medical staff persists in maintaining that comprehensive care consists only of an "attitude," whereas the psychologist maintains that areas of special knowledge in behavioral sciences should constitute an important part of the comprehensively-oriented physician. It is obvious from the results that "attitude," such as it was, was not enough.

In spite of the deficiencies, the program, especially the experimental design and measurements phases, deserves high commendation and serious study by all medical educators.

W.S.

CURRENT VIRUS RESEARCH. Edited by C. H. ANDREWS. Pp. 75; 28 ills. London: Medical Department, the British Council, 1959. Price, $3.25.

THE September, 1959, issue of the British Medical Bulletin consisted solely of 15 review articles on selected topics in virology. Because eminent British authorities discuss important subjects such as interferon, arthropod-borne viruses, and virus genetics, perusal of this small paperback volume is a convenient and reliable way for the nonvirologist to keep abreast of recent developments. Apparently it can be ordered only from the British Medical Bulletin, 65 Davies Street, London, W. 1. E.S.

BIOPHYSICAL SCIENCE—A STUDY PROGRAM. Edited by J. L. ONCLEY, F. O. SCHMITT, R. C. WILLIAMS, M. D. ROSENBERG, AND R. H. BOLT. Pp. 606; 529 ills. New York: John Wilely & Sons, 1959. Price, $6.50.

THIS volume contains the integrated series of papers presented at the Study Program in Biophysical Science, Boulder, Colorado, July 20 to August 16, 1958. The 61 papers indicate in many fields how physical and chemical approaches to biology have combined to elucidate the life processes. The subjects span a considerable range from molecular biology, cellular responses, macromolecular systems, enzyme action, and the like, to hormone regulations and biological transducers and coding. The contributors are gifted scientists and senior researchers. The papers are short, well written, contain many concrete scientific data and broaden the base of common language and understanding among a heterogeneous group of biologists, physicists and chemists. G.H.

ANGIOLOGIE. Edited by PROF. DR. MAX RATSCHOW, Darmstadt. Pp. 831; 373 ills. Stuttgart: Georg Thieme Verlag, 1959 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $41.45.

THIS excellent book presents a comprehensive discussion by 26 experts of all conceivable aspects of general and special angiology. General angiology is divided into several chapters each on normal and pathological anatomy, physiology and pathophysiology, etiology and pathogenesis, general diagnostics and general therapy. Special angiology is divided into angioneuropathies and organic diseases of the vessels. The latter include arterial occlusions, allergic angiitides, arterio venous fistulae, arteriosclerosis, venous thrombosis, elephantiasis and related disorders, aneurysms. varices, angiomas and others. The last chapter deals with insurance medicine. Because of the arrangement of the material, certain aspects are discussed twice or thrice. Functional anatomy, for instance, is presented by Linzbach as well as by Staubesand, while the angiitides are discussed by Meyer and by Hieronymi as well as by Bock. Therefore, conceptual differences and even contradictions are apparent in places. But these appear to be advantageous rather than disadvantageous for they introduce the reader into the problematics in this field, and they sharpen his discernment. The book is superbly illustrated. The references are comprehensive with full coverage of the American literature. This reviewer recommends it highly to all physicians interested in angiology. W.E.

THE MOTHER-CHILD INTERACTION IN PSYCHOSOMATIC DISORDER. BY ANN M. GARNER AND CHARLES WENAR, University of Illinois. Pp. 290. Urbana, Ill.: University of Illinois Press, 1959. Price, $6.00.

THIS is a report of the psychological research designed to test the assumption that mothers of children who develop psychosomatic disorders lack "Motherliness" in caring

for their infants during the first year of life. "Motherliness" is defined as maternal gratification of the infant's needs for body care and pleasureable stimulation in ways that also provide the mother herself with satisfaction. The authors consider the subject from the standpoint of a quality in the mother, rather than a need of the infant.

These data are interpreted as confirming the basic assumption that the lack of motherliness predisposes the infant to a developmental aberation affecting both structure and function. The authors are of the opinion that the conditions giving rise to this are general rather than specific in contrast to the view of F. Alexander and further that these factors differ from those that predispose to Neurosis. The conclusion expressed here coincides with current opinion to the extent that the mother child interaction is considered crucial to the further development of the infant.

The emphasis on the negative effect of maternal frustration minimizes the vital role played by this force in promoting growth. The view that factors that predispose to a neurosis only occur later than the first year is neither in accord with Freudian theory nor with the clinical data on which Freudian theory is based. Psychosomatic Disorder and Neurotic Personality organization are not mutually exclusive states. W.R.

ACUTE PERICARDITIS. By DAVID H. SPODICK, M.D., Senior Physician and Chief, Cardiographic Laboratory of the Medical Services, Lemuel Shattuck Hospital. Pp. 182; 28 ills. New York and London: Grune & Stratton, Inc., 1959. Price, $6.50.

IN this monograph, a well written and organized review is made of the normal and diseased pericardium. Symptoms, signs and pathophysiology are presented, and diseases producing acute pericarditis are succinctly described. Less than 4 pages are devoted to constrictive pericarditis which is considered beyond the scope of this work. However, it is important to point out that pericardial calcification is insufficient evidence for a diagnosis of constrictive pericarditis. An obvious misspelling is in the heading for Chapter XXII. More than 361 references are given but several pertinent ones are omitted, particularly the role of the pericardium in protecting against ventriculo-atrial regurgitation which may account for the descending limb of Starling's curve. There is also too brief a discussion of special Roentgen-ray techniques which have contributed so much to the recognition and understanding of pericardial diseases. The intravenous injection of pure carbon dioxide is a simple screening method for rapid, easy recognition of involvement of the pericardial sac begging for wider usage, and sequential venous angiocardiography allows study of the entire cardiac silhouette and its contents, including flow through and within the heart. With the addition of cine-angiocardiography, motion of the heart and pericardium may be studied and various hypotheses based upon assumptions of differences in motion of the heart surrounded by fluid may be tested. Knowledge of the contents of this book and the use of these Roentgen-ray techniques can result only in an increased awareness and understanding of disorders affecting the pericardium. J.Z.

A TEXTBOOK OF MEDICINE. Edited by RUSSELL L. CECIL, M.D., Sc.D., Professor of Clinical Medicine Emeritus, Cornell University, and ROBERT F. LOEB, M.D., Sc.D., D.HON. CAUSA, LL.D., Bard Professor of Medicine, Columbia University College of Physicians and Surgeons. 10th ed. Pp. 1665; 182 ills. Philadelphia and London: W. B. Saunders Co., 1959. Price, $16.50.

ALL physicians will welcome this the tenth edition of an outstanding textbook of internal medicine. Its 1660 pages present what is probably the most compact coverage of the field of internal medicine today. It is the work of 164 contributors and it includes 36 topics not covered in the previous edition. The editors are to be congratulated upon their excellent collation of this extensive material. R.K.

TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, M.D., HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., AND ALEXANDER MARBLE, M.D., New England Deaconess Hosital, Boston. 10th ed. Pp. 798; illustrated. Philadelphia: Lea & Febiger, 1959. Price, $16.50.

THE medical profession will welcome with enthusiasm the 10th edition of this outstanding text on the treatment of diabetes mellitus. Its great value depends, in large measure, on the outstanding experience and critical analysis of case material in the hands of Doctor Joslin and his associates, a total of 52,560 patients. Thus the new edition presents the oral treatment of diabetes as based on their experience with at least 3,000 patients. Then there is the matter of continuity,

in that Doctor Joslin, who brought out the first edition in 1916, continues to be active. This is indeed a classic among medical textbooks. R.K.

U.S. Army in World War II. The Technical Services. The Medical Department: Hospitalizatoin and Evacuation, Zone of Interior. By Clarence McKittrich Smith. Pp. 503; 28 ills. Washington: Office of the Chief of Military History, Department of the Army, 1956. Price, $4.00.

This volume deals primarily with the logistics of hospital organization and evacuation. Moreover it is concerned largely with the events within the Continental United States. Part I has chapters on organization and responsibilities for hospitalization, on planning for and expanding hospitals in the United States and on plans and preparations for hospitalization in overseas areas. Part II deals with hospitalization in the early war years from December, 1941, to mid 1943. Part III considers hospitalization in the later war years and Part IV is primarily concerned with evacuation procedures. In addition to its historical value, there is here available a wealth of material for all administrative and medical service corps officers as well as medical officers in the present military establishment. In the last section there is an interesting chapter on evacuation by sea when the Army had its first major experience with its own hospital ships, or, as they might have been more properly named, hospital ambulance ships. R.K.

Preventive Medicine in World War II. Vol. IV. Communicable Diseases. Edited by Col. John Boyd Coates, Jr., MC, USA. Pp. 544; 52 ills. Washington: Office of the Surgeon General, Department of the Army, 1958. Price, $5.50.

The prevention and control of communicable diseases constitutes a major segment of the general mission of the Medical Department of the Army. It is in this that field military medicine has achieved some of its greatest triumphs. In the Spanish American War five soldiers died of disease for every one who was killed in battle. In World War II, the ratio was 0.07 to 1. These triumphs have accrued to the benefit of civilian medicine. This volume, therefore, deserves study by all who are interested in preventive medicine. The present volume deals with diseases transmitted chiefly through the respiratory tract including the common viral infections, diphtheria, meningococcus infections, the pneumonias, tuberculosis and coccidiodal mycosis; also diseases transmitted chiefly through the alimentary tract including food poisons, brucellosis, cholera, typhoid and paratyphoid fevers, amebiasis, nematode and cestode infections. R.K.

The Foot and Ankle. By Philip Lewin, M.D., Professor Emeritus of Bone and Joint Surgery, Northwestern University Medical School. 4th ed. Pp. 612; 339 ills. Philadelphia: Lea & Febiger, 1959. Price, $14.00.

This reviewer has referred to this text since 1940. To the reviewer this latest edition gave the same pleasure as discussing old pleasures with a tried and true friend. The text is complete. It deals not only with clinical problems and their management but in a succinct manner clearly explains the basic anatomy, physiology and biomechanics of the foot and ankle.

The scope of afflictions is wide and varied. Surgical and nonsurgical therapy is well handled. Important too are afflictions of the foot secondary to generalized medical diseases as seen in deficiency diseases and metabolic and glandular diseases.

The text is well printed and copiously illustrated. It is unhesitatingly recommended for students of medicine or nursing as well as general practitioners and chiropodists. Among orthopedists it can be considered a must. A.S.

Helminthen und Helminthiasen des Menschen. By Prof. Dr. med. Rudolf Wigand and Prof. Dr. Otto Mattes. Pp. 474; 130 ills. Jena: Gustav Fischer, 1958. Price, DM 31.60.

The first 300 pages of this work deal with the helminths which are parasitic for man, beginning with a chapter on the general subject of parasites and parasitism and the methods of examination and recognition, and continuing with descriptions of the several types of worms. The remainder of the volume is given to the clinical aspects of human infestations. This, too, begins with a general section on diagnostic procedures, the control of therapy, the allergic reactions of the host, the materia medica involved, and then continues with a description of the several infestations. It should be emphasized that the coverage is world-wide in its scope. There are numerous excellent illustrations. Those who read German will find here a wealth of excellent biological and clinical material. R.K.

SURGERY OF THE FOOT. By HENRI L. DUVRIES, M.D., Clinical Instructor in Surgery, Chicago Medical School; Attending Surgeon, Columbus Hospital, Mother Cabrini Hospital and Frank Cuneo Hospital; Chairman, Department of Surgery, Illinois College of Chiropody and Foot Surgery, Chicago. Pp. 494; 403 ills. St. Louis: C. V. Mosby Co., 1959. Price, $12.50.

THIS text is encyclopedic in scope. Unfortunately it suffers the limitations of an encyclopedia being impersonal and lacking positive opinion where controversial subjects demand it. His authority comes through best in the chiropodial aspects of the text. Even here one might find fault with several of the operations labeled "DuVries' Technique" which are often a surgical approach, elimination of a deformity, and a closure.

Most orthopedic surgeons would rather not see correction of hammer toes, removal of small tumors or cysts of the foot, or phalangeal capsulotomies accomplished in the office as recommended. The use of Roentgen-ray therapy for plantar warts and hyperkeratotic lesions is certainly debatable. It is unfortunate in his chapter on examination that the passive motions in the intertarsal joints are not more carefully outlined. Plantar fibromatosis is not synonymous with Dupuytren's contracture, and his concept of Volkmann's ischemic contracture and Garre's sclerosing osteitis is not in complete concordance with general medical thinking. His discourse on anesthesia should discuss the dangers therein, particularly the use of epinephrine to potentiate local anesthesia. Most illustrations are good particularly some of the photographs in the chapter on anomalies and congenital defects. The diagnosis of Sever's Disease on Figure 256 would appear to be wrong, and the label on Figure 168 "Ainhum's Disease" is incorrect.

The inclusion in the text of a chapter on tumors, nervous disorders, and fractures would appear to be unnecessary overspecialization in view of the availability of excellent texts devoted to these lesions. His passages on shoes are particularly noteworthy. The bibliography is complete and throughout the text the author makes repeated references to articles by other workers in the field.

This text should be available in reference libraries to workers interested in the field.

H.S.

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